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Phytocannabinoids

Afeef S. Husni and Stephen J. Cutler
University of Mississippi, USA

1. Introduction

What is marijuana? Marijuana, also known as *Cannabis*, is defined as any preparation of the *Cannabis sativa* plant used to exploit psychoactive effects whether it is recreational or medicinal. According to the 2004 World Drug Report, 3.7% of the population 15-64 years of age consumed marijuana from 2001-2003 (World Drug Report, 2004). The use of marijuana is associated with numerous pharmacological effects; most, but not all may attributed to tetrahydrocannabinol (THC). The combination of THC and other compounds from *Cannabis sativa* may all exhibit specific pharmacological effects. These isolates from *Cannabis* are known as cannabinoids (ElSohly, 2010).

Cannabinoids are a chemical class of C_{21} terpenophenolic compounds that represent a group of compounds found in *Cannabis sativa* (Mechoulam & Gaoni, 1967). Phytocannabinoids are the naturally occurring cannabinoids from *Cannabis* sp (Pate, 1999). It is now known that at least 85 cannabinoids have been derived from *Cannabis sativa* (El-Alfy et al., 2010). It is also known that some of these compounds are of medical importance in today's society.

In order to gain a better understanding of the pharmacological effects of the phytocannabinoids, human and rodent receptors are used to evaluate binding affinity of these compounds to two cannabinoid receptors that have been reported in literature, CB_1 and CB_2. CB_1 receptors are located mainly in the brain, while CB_2 receptors are primarily

peripheral and found on mature B cells and macrophages within the tonsils and spleen (Raymon & Walls, 2010). When activated, the CB_1 receptors exhibit the psychoactive effects caused by *Cannabis* use. Since CB_1 receptors are not present in the medulla oblongata, part of the brain stem responsible for respiratory and cardiovascular functions, there is not a risk of overdose resulting in respiratory depression or cardiovascular failure that may be seen with abuse of other drugs, such as the opioids. CB_2 receptors are said to be responsible for anti-inflammatory effects.

2. Cannabinoid receptor function

Cannabinoid receptors are G-protein coupled receptors (Figure 1), which are a large family of seven member transmembrane receptors that act in a second messenger fashion. When cannabinoid receptors are activated, they inhibit the enzyme adenylate cyclase. Adenylate cyclase is responsible for breaking ATP to form cyclic AMP (cAMP). When a ligand binds to the extracellular surface of cannabinoid receptors, it causes a conformational change of the receptor. This change activates the second messenger by exchanging guanosine diphosphate (GDP) for guanosine triphosphate (GTP). Then, the G-protein's alpha subunit separates from the beta/gamma subunit to cause intracellular proteins to function properly. In CB_1 and CB_2 receptors, cAMP acts as the second messenger. When these receptors are activated, cAMP levels decrease within the cell. Therefore, the result of activating cannabinoid receptors leads to a decrease in cAMP levels, and in turn leads to an inhibition of function.

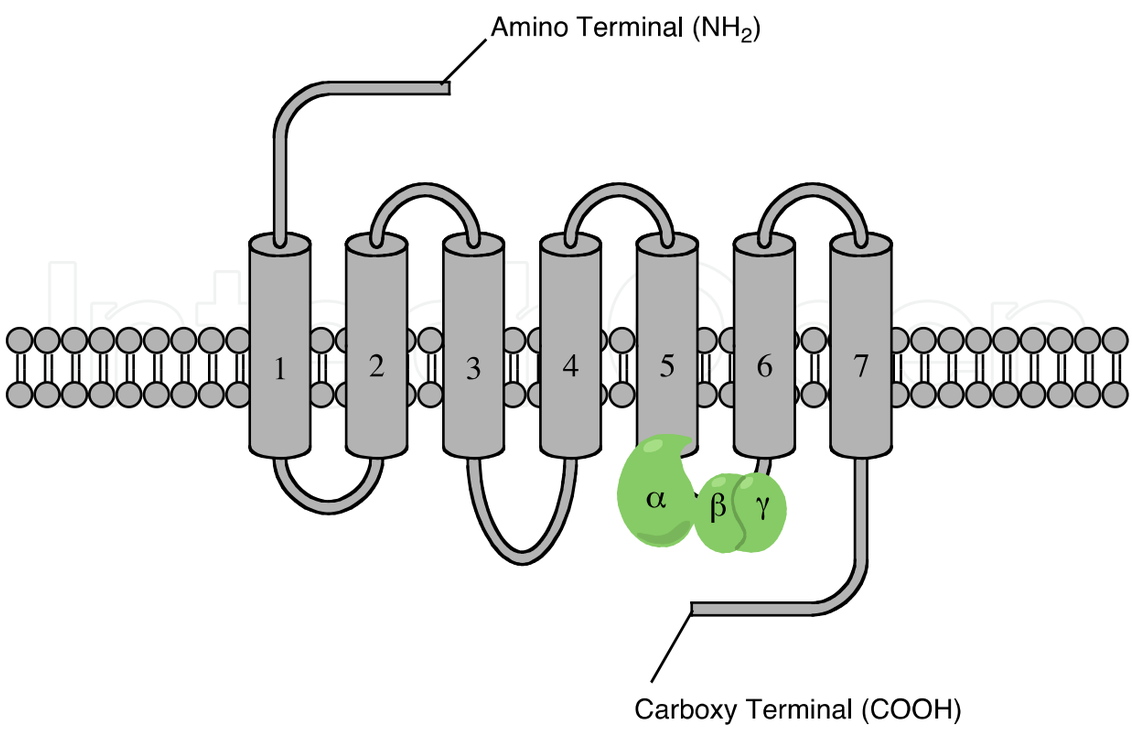

Fig. 1. Example of a G-Protein Coupled Receptor.

3. Endocannabinoids

Endogenous cannabinoids, or endocannabinoids, are substances produced in the body that activate the cannabinoid receptors. Generally, neurotransmitters are released presynaptically and activate the receptors on a postsynaptic cell. However, unlike most neurotransmitters, the endocannabinoids work in a reverse fashion. Endocannabinoids use retrograde signaling to achieve cannabinoid receptor activation. This means that the ligands are being produced postsynaptically, but acting presynaptically (Lambert, 2009). Another critical point in understanding the function of the endocannabinoids is that the endocannabinoid system can produce endocannabinoids "on demand" in response to an increase in intracellular calcium levels (Sugiura et al., 2006).

Shortly after the cloning of the cannabinoid receptors, researchers began searching for endogenous ligands that activate these receptors. The first endocannabinoid discovered was anandamide (Figure 2) in 1992 (Devane et al., 1992). Several years after the discovery of anandamide the second endogenous ligand, 2-arachadonoyl-glycerol (2-AG, Figure 3), was discovered (Sugiura et al., 2006). Anandamide and 2-AG act as a partial agonist and full agonist, respectively, at the CB_1 and CB_2 receptors. Although the structure of anandamide differs significantly from THC, both of these ligands have similar pharmacological profiles (Grotenhermen, 2002). Understanding the mechanism of how cannabinoids produce their effects is in part because of the discovery of the endocannabinoid system.

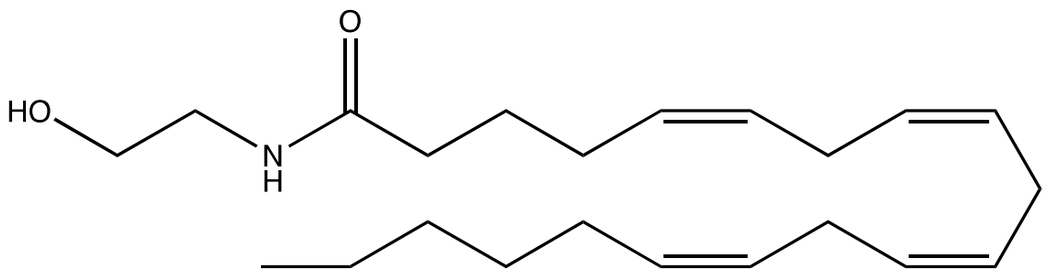

Fig. 2. Chemical structure of anandamide.

Although the physiological roles of the endocannabinoids are not fully defined, several pharmacological functions have been described. Studies suggest that these endogenous ligands may aid in pain relief, enhancement of appetite, blood pressure lowering during shock, embryonic development, and blocking of working memory (ElSohly, 2010).

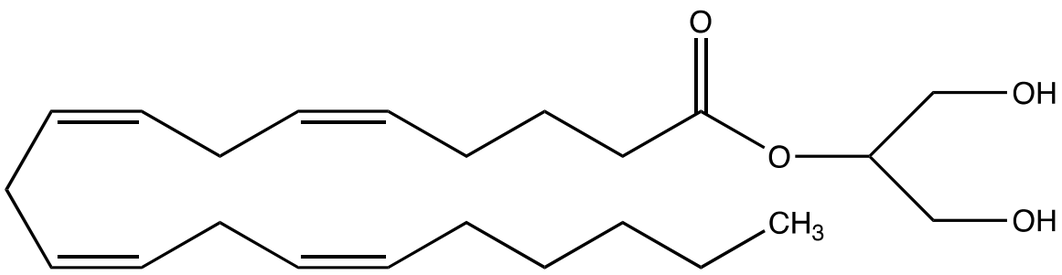

Fig. 3. Chemical structure of 2-AG.

4. Phytocannabinoids

The first cannabinoid identified was cannabigerol, and its precursor cannabigeric acid was shown to be the cannabinoid formed in the plant as well as endogenously (Yamauchi, 1975). Today, the most discussed phytocannabinoid is delta-9-tetrahydrocannabinol. In 1964, Gaoni and Mechoulam isolated and elucidated the chemical structure of THC from the leaves of *Cannabis sativa* (Mechoulam & Gaoni, 1964). THC is pharmacologically and toxicologically the best studied constituent of *Cannabis*, responsible for most of the psychoactive effects of natural *Cannabis* preparations (Grotenhermen, 2002). THC and cannabidiol (CBD) are the two most common naturally occurring cannabinoids.

As mentioned earlier, THC (Figure 4) is the main component of *Cannabis* responsible for the psychoactive effects. Other than *Cannabis* being abused to achieve a state of euphoria, it is now being used medicinally to aid in acquired immunodeficiency syndrome (AIDS) patients with wasting syndrome and for pain management, nausea, and vomiting associated with patients receiving cancer chemotherapy. Since THC is responsible for the psychoactive effects of *Cannabis*, people have learned how to genetically increase the concentration of THC within each plant to produce a stronger "high." Since 1980, the concentration of THC within marijuana has increased from less than 1.5% to approximately 20% (ElSohly et al., 2000). THC acts a partial agonist at the CB_1 and CB_2 receptors, but functions via interaction with the CB_1 receptor.

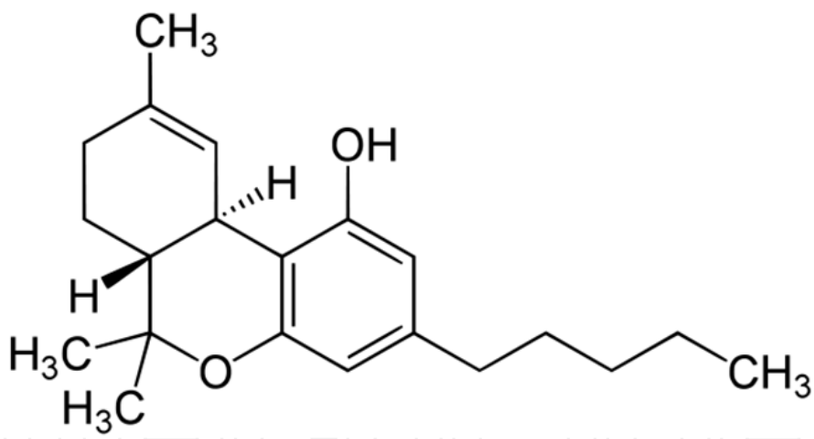

Fig. 4. Chemical structure of delta-9-THC.

The second major constituent of *Cannabis*, cannabidiol (CBD, Figure 5), is responsible for the anti-inflammatory effects due to its interactions with the human CB_2 receptor. CBD was first isolated in 1940 (Adams et al., 1940); however, it was not until 1963 that Mechoulam and Shvo elucidated its correct structure (Mechoulam & Shvo, 1963). At the human CB_2 receptor, CBD's mechanism of action shows inverse agonism activity (Pertwee et al., 2007). In 1995, Benet and colleagues show that cannabidiol is not only responsible for anti-inflammatory effects, but may also aid in reducing unpleasant side effects from THC, including reduced anxiety (Benet et al., 1995). They found that CBD inhibits cytochrome P450 3A11, which causes THC to change into its more potent metabolite 11-hydroxy-THC (Gallily et al., 2002).

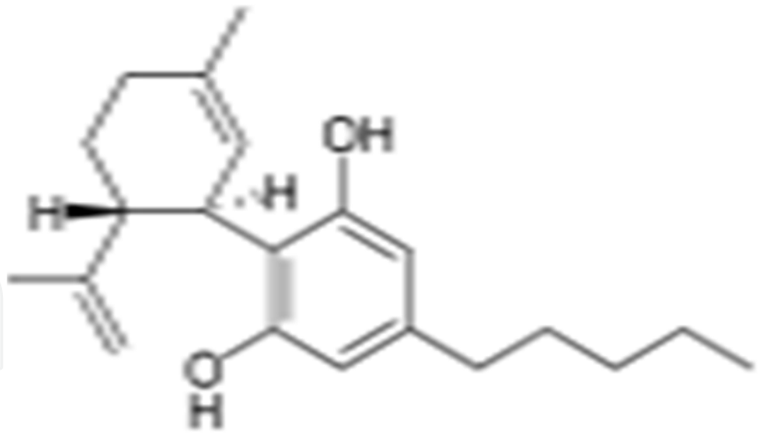

Fig. 5. Chemical structure of cannabidiol.

Tetrahydrocannabinol and cannabidiol are the two most discussed phytocannabinoids, but not the only ones known. ElSohly and co-investigators have divided the phytocannabinoids into ten subclasses: 1) Cannabigerol type – propyl side chains and monomethyl ether derivatives 2) Cannabichromene type – analogs present in the C-5 position 3) Cannabidiol type – analogs varying from C-1 to C-5 positions 4) Delta-9-tetrahydrocannabinol type – double bond in the C-9 position; responsible for psychoactive effects 5) Delta-8-tetrahydrocannabinol type – double bond in the C-8 position; thermodynamically more stable than delta-9-THC , however, 20% less active 6) Cannabicyclol type – five atom ring and C-1 bridge 7) Cannabielsoin type – artifacts formed from CBD 8) Cannabinol and Cannabinodiol types – A ring aromatization 9) Cannabitriol type – additional hydroxyl substitution 10) Miscellaneous types – ex: furano ring, carbonyl function, tetrahydroxy substitution (ElSohly, 2010).

Another phytocannabinoid that shows a significant amount of importance is cannabinol (CBN, Figure 6); it is a metabolite of tetrahydrocannabinol. It was the first cannabinoid identified from *Cannabis sativa*. (Wood et al., 1896). Along with THC, cannabinol is also a psychoactive component of *Cannabis* due to its interaction with CB_1 receptors. Compared to THC, it acts a weak agonist at both the CB_1 and CB_2 receptors.

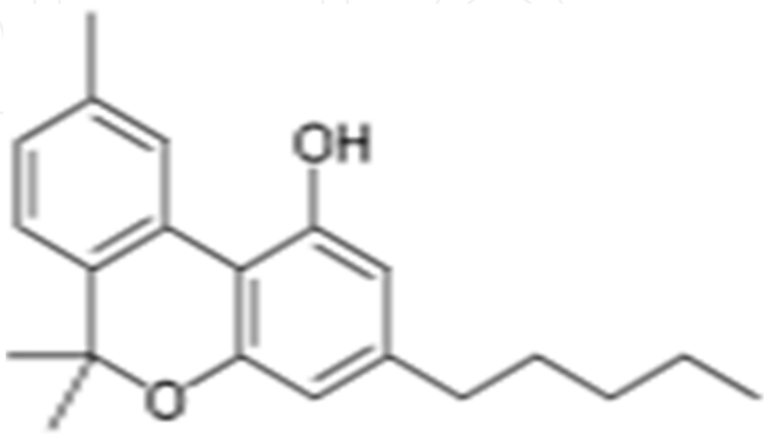

Fig. 6. Chemical structure of cannabinol.

Extracts that have been isolated from marijuana may be tested to see if they have affinity for each of the CB_1- or CB_2- type receptors. THC remains the best phytocannabinoid in terms of affinity for the cannabinoid receptors with a binding Ki of 14nM (Figure 7). Most of the compounds isolated from *Cannabis* show a sufficient amount of binding activity at both of the cannabinoid receptors. However, not all compounds isolated show interactions with either CB_1 or CB_2. For instance, even though cannabidiol is a major constituent of *Cannabis* and shows pharmacological effects, it has little or no activity for CB_1 or CB_2 receptors (Mechoulam & Rodriguez, 2007). To determine binding affinity and functional activity, in vitro assays are performed.

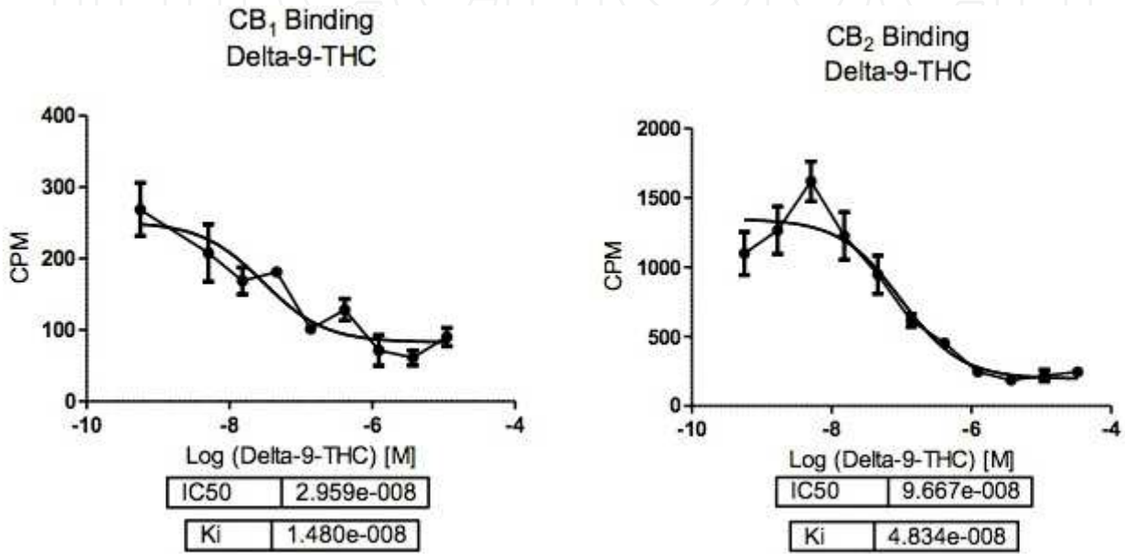

Fig. 7. Binding affinity of delta-9-THC at Cannabinoid Receptor 1 and Cannabinoid Receptor 2.

5. *In vitro* bioassays

In order to have success with in vitro assays, cultured cells containing the specific receptors must be developed. At the University of Mississippi HEK293 cells have been transfected with full length human CB_1 and human CB_2 DNA via electroporation. Once "shocked," the cells open and accept the human CB_1 and CB_2 cDNA with a linked specific antibiotic resistant plasmid. Since not all cells will receive the DNA, a selection process using the specific antibiotic is added to the cultured cells in order to kill off cells without the cDNA. After an allotted time period for growth, a single cell is selected and clonal colonies are grown in cell culture. The replication of a single cell containing either CB_1 or CB_2 DNA allows researchers to guarantee the over expression of cannabinoid receptors on the cell membrane. With this, mass subculture followed by "scraping" of the cells leads to the membrane with the receptors. Once the protein concentration is determined this membrane may be used for in vitro assays.

Phytocannabinoids may be tested for their binding affinity toward each of the cannabinoid receptors. A competitive binding assay is done to determine the binding affinity of each compound. The competition is between the chosen phytocannabinoid and a labeled ligand, such as ^{3}H- CP-55, 940. It is known that the labeled ligand will tightly bind to each of the cannabinoid receptors; therefore, if a test compound shows affinity for the receptors, the

amount of labeled ligand bound to the receptor will be low resulting in high binding affinity of the test compound. A compound showing strong binding affinity for either of the cannabinoid receptors, warrants testing to determine the functional activity.

A functional assay determines whether the compound is acting as an agonist, antagonist, or inverse agonist. As opposed to the binding assay, an in vitro functional assay is not based upon competitive binding, but rather "tracking" the amounts of guanosine triphosphate (GTP). When the membrane is not stimulated, there is a pool of guanosine diphosphate (GDP) associated with it. Upon stimulation, this pool of GDP is converted into GTP. To monitor this response, ^{35}S labeled GTP is added to the assay to bind to the receptors. Therefore, an increase in GTP is directly proportional to stimulation of the receptor by labeled ligand. An agonist compound is indicated by an increase in GTP. Delta-9-THC has a functional Ki of approximately 300nM, which means it is acting as a partial agonist, yet is still responsible for the psychoactive effects associated with *Cannabis* (Figure 8). To detect an antagonist, the compound must be tested in the presence of a known agonist at that specific receptor. The antagonist blocks the ability of the agonist to fully stimulate the receptor, thus resulting in a right shift of the agonist EC_{50}.

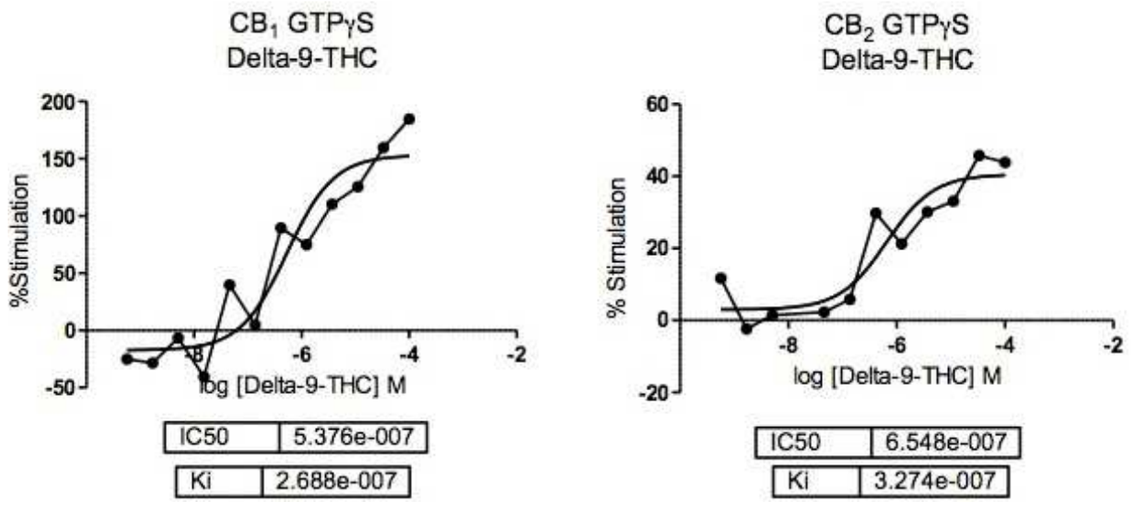

Fig. 8. Functional assay activity of delta-9-THC at Cannabinoid Receptor 1 and Cannabinoid Receptor 2.

6. *In Vivo* bioassays

Cannabinoids that show promising activity in the functional assay, whether acting as an agonist or antagonist, may be tested in vivo using the tetrad assay in mice. In the late 1980s, Little and his colleagues began testing rodents treated with cannabinoids in this tetrad assay. The term tetrad describes a series of four different tests to help evaluate the biological effects of a compound: 1) Locomotor activity 2) Catalepsy 3) Hypothermia and 4) Analgesia. The locomotor activity test allows a researcher to determine if the rodent is acting "lazy." The rodent is placed in a box with perpendicular gridlines, which are beams of light. The test determines the amount of times the beams are broken in an allotted time period, an increase in the number of times broken correlates with a decrease in locomotor activity. To determine if the drug causes cataleptic effects, a rodent is placed on a bar elevated off the ground surface. If

the rodent remains immobile, it is considered cataleptic. Hypothermia, also know as a rectal temperature assay, is simply a measure of the rodents rectal temperature after the drug has been administered. For the last part of the tetrad assay, there are two different methods of testing for analgesic effects. One method is the hot plate (Figure 9) assay. In this assay, a rodent is placed upon a hot plate and the time it takes for the rodent to react, usually a small jump, is recorded. The second method is known as the tail-flick assay. In this assay, the rodent is immobilized and a high temperature beam of light is sporadically placed on the tail. If the rodent feels pain, it will move its tail either left or right (Little, 1988).

Fig. 9. Analgesic portion of tetrad assay: hot plate test.

7. Medicinal uses of marijuana

According the United Nations, *Cannabis* "is the most widely used illicit substance in the world" (World Drug Report, 2010). There are people who use Cannabis medicinally, and there are others who abuse *Cannabis* in order get "high," or obtain a state of euphoria. Those who use marijuana regularly for medicinal purposes use strict, smaller amounts to control the strength and duration of the "high." However, those who abuse marijuana attempt to smoke or ingest as much as necessary to achieve their own personal state of euphoria. This abuse negatively affects the people who do need *Cannabis* to help with side effects of chemotherapy and AIDS. *Cannabis* is not only used to help those suffering from cancer chemotherapy and AIDS, but it also lowers intraocular eye pressure for those with glaucoma, acts a pain reliever, and more recently has been found to help with symptoms of multiple sclerosis and depression. Therefore, researchers are attempting to formulate a synthetic cannabinoid that resembles the compounds isolated from *Cannabis*, but do not exploit psychotropic properties.

The goal of research in this area is to synthesize a cannabinoid-like compound that warrants a high affinity for either CB_1 or CB_2 receptors, or both, and can help patients without causing some of the unwanted side effects of marijuana, such as the psychotropic effects associated with CB_1. With this said, studies show that *Cannabis* users have fewer psychological side effects than those users administering synthetic THC. There are two synthetic cannabinoid products available on the market in the United States, Nabilone and Dronabinol (Figure 10). Some of these side effects from synthetic cannabinoids include dysphoria, depersonalization, anxiety, and paranoia (Grinsponn & Bakalar, 1997). As previously

mentioned, CBD has shown to reduce anxiety and other unpleasant side effects caused by ingestion of pure THC (Zuardi et al., 1982). The preference of whole *Cannabis* over synthetic formulations of THC is due to the lack of extra side effects associated with the whole *Cannabis*. This opens the door for scientists to study what is actually causing all of the side effects associated with synthetic THC. This also shows that some of the compounds associated with *Cannabis sativa* may be working synergistically to alleviate unwanted effects from THC when used alone (McPartland & Russo, 2001). So, the ultimate goal in cannabinoid drug development would be to mimic the non-psychotropic effects associated with CB_1, mimic the beneficial effects associated with CB_2, and not deal with the negative side effects associated with marijuana or synthetic THC.

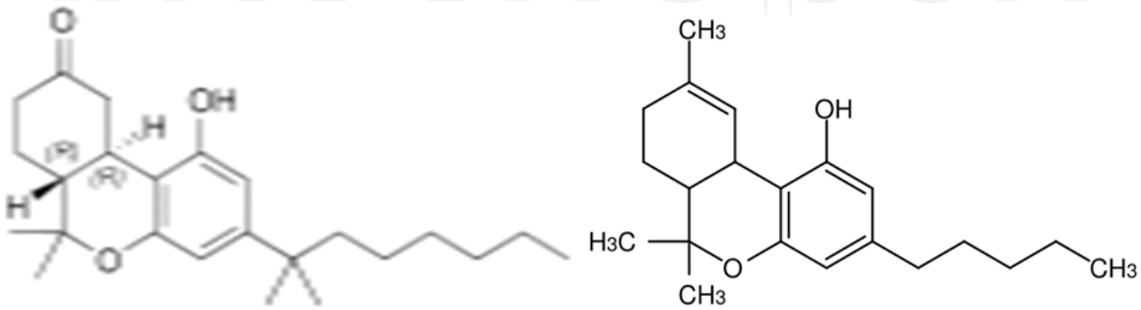

Fig. 10. Chemical structures of Nabilone (left) and Dronabinol (right).

8. Phytocannabinoids and depression

Depression may be described as a mood disorder associated with feeling down, sad, angry, or lost that interferes with everyday life. The most commonly associated drug categories for the treatment of depression include monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), selective-serotonin reuptake inhibitors (SSRIs), and serotonin-norepinephrine reuptake inhibitors (SNRIs). A new field of research involving *Cannabis* may be the link to the treatment of depression. However, studies show conflicting data as to whether *cannabis* is beneficial (Grinsponn & Balkar, 1998) or detrimental for the treatment of depression (Bovassa, 2001). Due to the conflicting results of these studies, Witkin switched the focus to the role of the endocannabinoid system and the treatment of depression from exogenously administered cannabinoids (Witkin et al., 2005). Since 2005, it has been concluded that the endocannabinoid system does play a role in the treatment of depression, but differs from minor depression to major depression.

New research has found that a common characteristic of *Cannabis*, mood elevation, may be the link to the treatment of depression. A study published by El-Alfy and co-investigators in 2010 describes the antidepressant effects associated with administration of phytocannabinoids. The objective of this study was to isolate the major cannabinoids from *Cannabis* and evaluate the antidepressant effects using the mouse forced swim test (FST), followed by the tail suspension test (TST). Typically in mice, when cannabinoids are administered they exert hypothermia and catalepsy, which means that a psychoactive state is being achieved. For these depression studies, only low dosages of these phytocannabinoids were administered so that the test subjects did not demonstrate psychoactive effects. The cannabinoids isolated and tested were cannabigerol (CBG), cannabinol (CBN), cannabichromene (CBC), cannabidiol (CBD), delta-8-THC, and delta-9-THC (THC) (Figure 12).

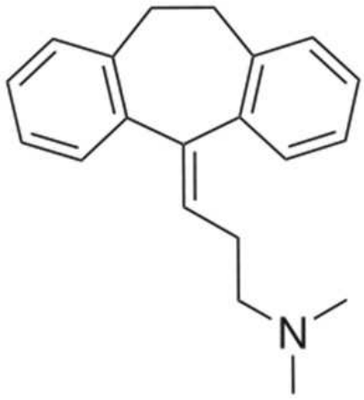

Fig. 11. Chemical structure of the tricyclic antidepressant, Amitriptyline.

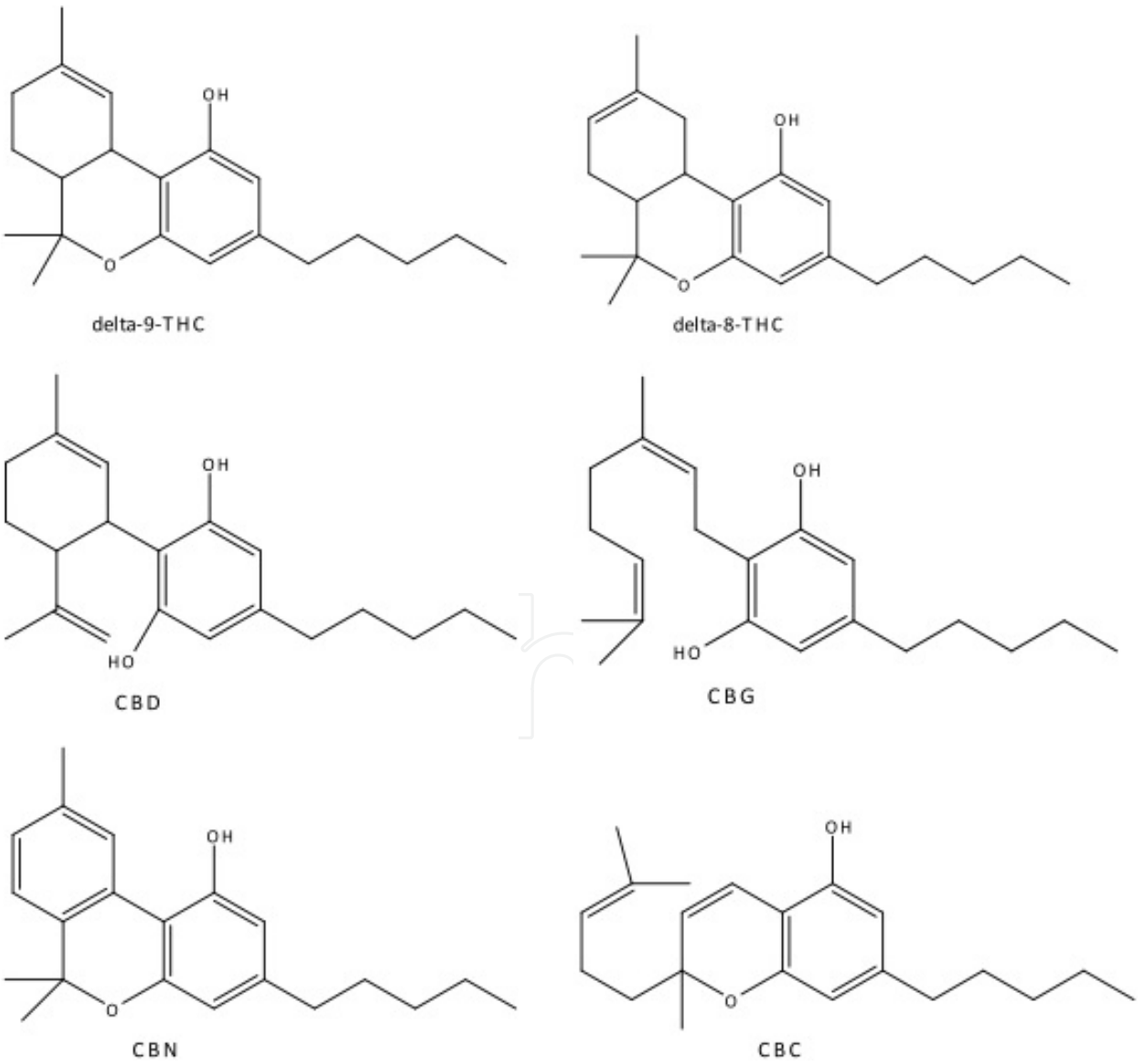

Fig. 12. The six phytocannabinoids tested for antidepressant-like effects (El-Alfy et al., 2010).

To assess that hypothermia and catalepsy were not achieved, the tetrad assay was completed after administration of each cannabinoid. Out of the six cannabinoids tested, only delta-8-THC and delta-9-THC showed a U-shaped dose response in the forced swim test. With this, only delta-9-THC showed significant antidepressant-like effects. Administration of the non-psychoactive components revealed that CBC and CBD displayed antidepressant-like effects in the forced swim test. However, a high dose of CBD was used to display these antidepressant-like effects.

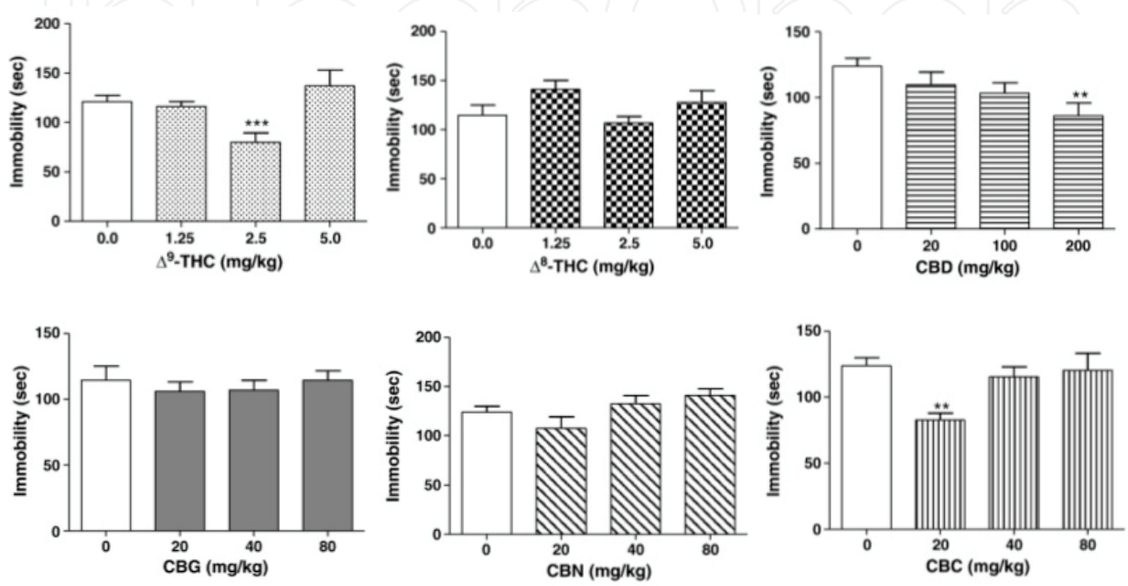

Fig. 13. Effects of each phytocannabinoid on immobility time in the mouse forced swim test (El-Alfy et al., 2010).

To further confirm these tests, delta-9-THC and CBC were evaluated in the tail suspension test. Between these two phytocannabinoids, only delta-9-THC continued to exhibit these antidepressant-like effects at low doses. Therefore, the results of this study show that delta-9-THC and other phytocannabinoids administered exogenously do indeed aid with the treatment of depression (El-Alfy et al., 2010).

9. Phytocannabinoids and appetite stimulation

Patients suffering from AIDS are now becoming the main target for the therapeutic use of *Cannabis*. Those with AIDS tend to lose their desire to eat regularly throughout the day. When this occurs, the patient becomes weak, agitated, tired, and anorexic; this occurrence in known as Wasting Syndrome. Research shows that at least 90% of patients who smoked marijuana had the desire to eat immediately after use (Haines & Green, 1970). With the use of *Cannabis* as a therapeutic drug to stimulate appetite, the suffering patients may be able to eat on a regular basis throughout the day, thus improving their quality of life. Several studies have shown that the use of marijuana does increase appetite, which also increases energy in daily life routines.

In a study conducted by Mattes and colleagues, the appetite stimulating effects of cannabinoids, specifically THC, were examined. A major focus in this study, for a means of clarification from previous research, was the route of administration of THC. The four

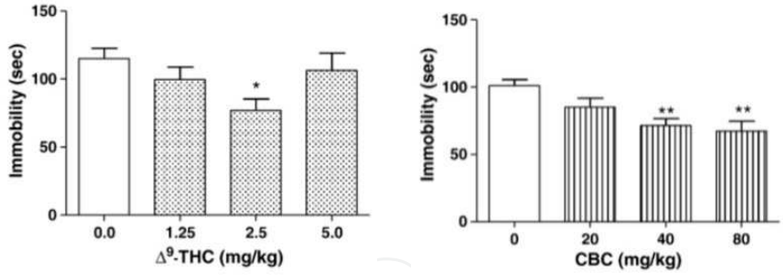

Fig. 14. Effects of THC and CBC on immobility time in the mouse tail suspension test (El-Alfy et al., 2010).

different ways in which THC was administered includes oral, inhaled, sublingual, and suppository. There are high levels of variability in determining if THC does actually stimulate appetite. Factors such as environment, age, gender, tolerance, dosage, and social influences play a role in the effect of THC on appetite. During one study, the suppository route of administration resulted in the highest energy intake when compared to oral, sublingual, and inhaled administration of THC (Figure 15).

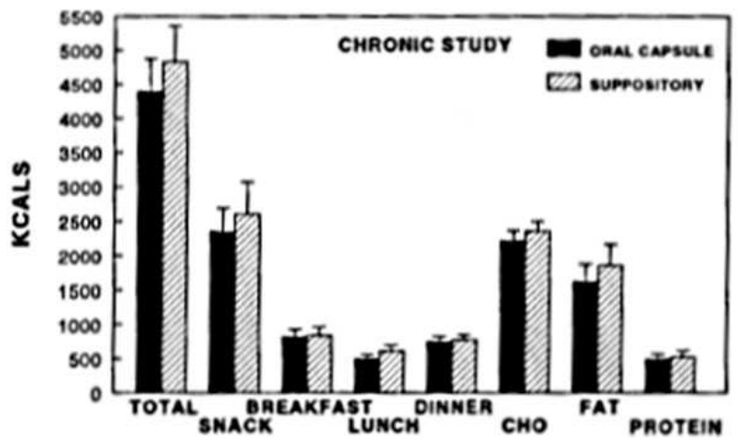

Fig. 15. Mean data from patients dosed orally and via suppository over a 72 hour time period (Mattes et al., 1994).

There is no single outcome on the effect of THC on appetite stimulation no matter the form of administration. The results vary from having no effect to the possibility of having major food cravings. In some circumstances, not only did the food cravings become increased, but during a meal the food seemed to also have an increased taste of delightfulness. The conclusion of this study indicates that THC as an appetite stimulant produces its highest effects on healthy, adult individuals who use low dosage amounts (Mattes et al., 1994).

10. Future directions

The growing population is becoming more aware of *Cannabis* as a medicinal plant, and not only a recreational drug. The first *Cannabis* publications date back to the early 1940's in which there was only one publication from 1940-1949. Today, when a search is performed there are over 7,000 journal articles that discuss anything associated with the words *Cannabis*, cannabinoids, or endocannabinoids. Over the last 50 years, marijuana has become

the most widely used illegal drug, along with one of the most widely studied plants. There are still many questions to be answered within the *Cannabis* field of study.

It is possible that the cannabinoid system has several other receptors that may explain the mechanism of action of compounds that exhibit cannabinoid-like effects when there is little or no affinity for CB_1 or CB_2. GPR55 and GPR119, both G-protein coupled receptors, are said to be novel cannabinoid receptors. All cannabinoid receptor antagonists appear to act as inverse agonists instead of neutral antagonists. There are few ligands starting to appear in literature as being neutral antagonists. Interest in this area could is important to help develop pharmacological tools to aid in finding neutral antagonists. These findings may possess unknown therapeutic advantages over receptor antagonists that act as inverse agonists (Pertwee, 2005).

It is now known that phytocannabinoids interact with the CB_1 and CB_2 receptors, and that the human body consists of an endocannabinoid system that activates these two receptors. However, what these receptors look like remains a mystery. A general structure-activity relationship has been determined for the cannabinoids, but there is no limitation to synthesizing new compounds that will interact strongly with these receptors. In *vitro* and in *vivo* bioassays play a crucial role in determining the affinities and functions of compounds associated with the CB_1 and CB_2 receptors. The information determined from these bioassays will continue to help develop novel therapeutic drugs that potentially have pharmacological effects related to *Cannabis* without the deleterious side effects.

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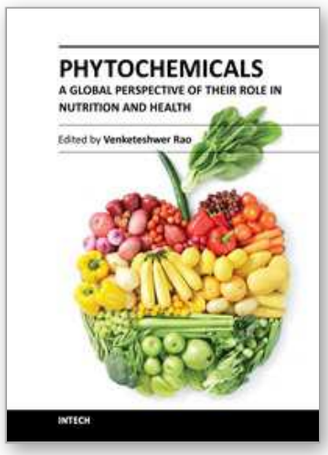

Phytochemicals - A Global Perspective of Their Role in Nutrition and Health

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Phytochemicals are biologically active compounds present in plants used for food and medicine. A great deal of interest has been generated recently in the isolation, characterization and biological activity of these phytochemicals. This book is in response to the need for more current and global scope of phytochemicals. It contains chapters written by internationally recognized authors. The topics covered in the book range from their occurrence, chemical and physical characteristics, analytical procedures, biological activity, safety and industrial applications. The book has been planned to meet the needs of the researchers, health professionals, government regulatory agencies and industries. This book will serve as a standard reference book in this important and fast growing area of phytochemicals, human nutrition and health.

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