A recent history of prejudice against the cannabis plant has led to a negative perception of the effects of cannabis on the human body. Current news and legislation are throwing the use of medicinal cannabis back into question— is it as bad as it seemed or is there medicinal potential from this plant?

The answer to the latter is a definite yes. The potential use of cannabis for medicinal application is seemingly endless and is now a huge area of interest for current pharmaceutics. Phytocannabinoids are cannabis-derived cannabinoids, and are the most commonly known bioactive group of cannabis compounds. There are estimated to be at least 150 cannabinoids made by the cannabis plant. Cannabinoids are a type of chemical compound that function as neurotransmitters in the human body. Until this point, research has focused only on the effects of a few more well-known cannabinoids; minimal research was performed to investigate the bioactivity of other available compounds in the plant. This paper aims to discuss the bioactivity of cannabinoids on the endocannabinoid system and highlight several cannabinoids that display potential for clinical applications.

THE ENDOCANNABINOID SYSTEM

In the 80s, an Israeli professor by the name of Raphael Mechoulam uncovered the structure of the first cannabinoid, Δ9-tetrahydrocannabinol (THC), shortly followed by cannabidiol (CBD). Discovery of these cannabinoids led Mechoulam to ponder the biochemical basis of their physiological effects and how it is that the human body can metabolize them at all. In 1988, Mechoulam found the first endocannabinoid receptor (CB1).

Mechoulam first discovered CB1 receptors in the brain and spinal cord, but later studies found some CB1 receptors are also found in some peripheral organs and tissues. It is of interest to note firstly that CB1 receptors are the most abundant neurotransmitter receptor found in the brain; secondly, the only part of the brain lacking CB1 receptors is the medulla oblongata, responsible for respiratory and cardiovascular function. Identification of CB1 was shortly followed by discovery of the second endocannabinoid receptor type CB2 in 1993. CB2 receptors are located on hematopoietic cells, white blood cells, and in the tonsils and spleen in a much greater quantity than of CB1.

Mechoulam was not satisfied with just the discovery of cannabinoid receptors; why would the human brain have in place receptors for exogenous chemical compounds? In 1992, 28 years after his discovery of THC, Mechoulam uncovered the structure of the first known endogenous human cannabinoid, anandamide (AEA). Discovering that this endocannabinoid exists confirmed the pre-existence of the endocannabinoid system (ECS) of endogenous neurotransmitters and receptors. The structure of THC so closely resembles AEA that it may bind in the same way AEA does to the both CB1 and CB2, and produce similar physiological effects. AEA is synthesized in areas of the brain that control memory and movement, and plays a role in creating connections between nerve cells, relating its function to learning and memory. Interestingly, anandamide is degraded to form arachidonic acid,
About Endocannabinoid Receptors

Endocannabinoid receptors are structures found on the surfaces of cells that recognize specific neurotransmitter molecules and allow them to bind to it. When a molecule binds to and activates a neurotransmitter receptor, it triggers a cascade of chemical and electrical signals that serve to communicate with other cells and produce a biological response.

Neurotransmitter receptors function when a signal molecule, or ligand, attaches to them. Cannabinoids are ligands to cannabinoid receptors. Ligands may act as either agonists or antagonists on neurotransmitter receptors, and may display different binding strength, or affinity, for that receptor. If a ligand is a receptor agonist, its binding will activate the receptor to trigger a physiological response. Antagonists will bind to a receptor but will occupy the binding site without stimulating the receptor in any way, creating no response. Depending on its affinity, a ligand can be either a partial or a full agonist. Ligand affinities and their resulting response are illustrated below.

Receptors are pictured in blue on the surface of the cell controlling an ion channel between them. Two ligands are shown, a partial agonist (yellow) and a full agonist (red).

a. With no ligand bound to the receptor, the ion channel remains closed and no physiological response occurs.
b. A full agonist binds with strong affinity to the receptor and fully activates it to produce a maximal response.
c. A partial agonist binds with low affinity to the receptor. Therefore, a higher relative concentration of partial agonist is required to achieve full receptor activation.
d. In the presence of a full agonist, a partial agonist effectively acts as an antagonist. It is unable to fully activate the receptor on its own, and blocks the full agonist from binding and achieving full activation. Therefore, only a partial response is achieved.
which is an essential fatty acid required for cognition and memory; arachidonic acid is also responsible for the first communications between mother and embryo during pregnancy. The effects of AEA are short lived as it is quickly metabolized, accounting for the lack of the same psychoactive ‘high’ that THC gives.

In 1995, Mechoulam’s team found the second known endocannabinoid, 2-arachidonoylglycerol (2-AG). 2-AG is a full agonist of both CB1 and CB2 and is the primary binding molecule for CB2. 2-AG is found more abundantly than AEA and plays a key role in regulation of appetite, pain, and the immune system. 2-AG has also been shown to play a role in inhibition of metastasizing cancers.

Although it remained undiscovered until recently, almost every living animal, excepting insects, has an ECS for receiving and metabolizing cannabinoids—whether they be endogenous, natural, or synthetic. The abundant presence of cannabinoid receptors throughout the brain and body has led scientists to believe the ECS to be the most important human signalling system, as it functions to regulate and maintain homeostasis in the body. Endocannabinoids regulate some of the most important processes in the human body including glucose metabolism, neuroprotection, and the immune response. Endocannabinoids are the only neurotransmitters to partake in ‘retrograde signalling’, which serves to calm excessive physiological activity. Through negative feedback, they calm other neurotransmitters from firing too quickly. For example, retrograde signalling is how the body quells the immune response at the correct point before allergic reaction occurs.

Studies have been performed to show precisely how important endocannabinoids are for human functioning. Deficiency in AEA has been shown to cause spontaneous abortion in mammals. Mice bred without cannabinoid receptors exhibited symptoms of babies with ‘failure to thrive’ syndrome where they withered and died prematurely. Endocannabinoid deficiencies have also been associated with an decreased or lack of ability to adapt to chronic stress. In cases of stroke, increased endocannabinoid levels were detected in the brain, showing the neuroprotective effects of the ECS, and providing actual evidence for a built-in repair kit in the human brain. Through an understanding of the ECS there is potential to manipulate cannabinoid receptors in a way such as to not only cure diseases but perhaps prevent them altogether.

**PHYTOCANNABINOID FORMATION**

Phytocannabinoids are naturally synthesized by the cannabis plant within its own tissues. The process begins when two molecules (substrates) join together in a synthesis reaction to form what is referred to as a precursor cannabinoid. Most phytocannabinoids derive from the same precursor cannabinoid, cannabigerolic acid (CBGA). CBGA is created from the synthesis of two substrates, olivetolic acid and geranyl pyrophosphate. CBGA will then undergo several different enzymatic transformations to form other cannabinoids, each of which can react further to create more cannabinoids. Though less common, there exist other precursor phytocannabinoids that follow their own degradation pathways to create more compounds. For example, geranyl pyrophosphate may also undergo synthesis with divarinolic acid to form cannabigerovarinic acid (CBGVA). CBGVA is a precursor cannabinoid which may undergo its own series of enzymatic reactions to form a different ‘family’ of cannabinoids.

Molecular transformations take place in response to environmental or external factors such as heat, UV rays, or exposure to oxygen. Therefore, as a cannabis plant ages, the initial CBGA or CBGVA in the plant will react to form new cannabinoids. The relative concentrations of each cannabinoid differ depending on the plant strain and its growing conditions. As each phytocannabinoid differs in structure and therefore bioactivity, different balances of phytocannabinoids in a plant will create a specific set of pharmaceutical effects. Generally, cannabinoids that bind with CB1 create psychoactive effects whereas cannabinoids that bind to CB2 tend to produce responses from the immune system. By gaining an understanding of cannabinoid structures and their catalysts for formation, cannabis sativa may be grown and harvested in such a way as to maximize the content of specific cannabinoids for use in pharmacology.
PHARMACOLOGICAL EFFECTS

As previously stated, CBGA is the precursor to most phytocannabinoids and is created through an enzymatic reaction. Further enzymatic reactions cause CBGA to cyclize into different derivatives, or, CBGA may undergo heat decarboxylation to form cannabigerol (CBG). CBG is a weak partial agonist for CB1 and CB2, but it does not have any psychoactive effects. Notably, CBG is a potent α-2 adrenoreceptor agonist, which stimulates a strong analgesic response. It has potent antibiotic and antifungal properties; CBG is even effective against methicillin-resistant staphylococcus aureus (mRSA). CBG functions to inhibit keratinocyte production, therefore making it useful in treatment of psoriasis. CBG is also an AEA uptake inhibitor, giving it use in memory enhancement and treatment of memory loss. Its anti-inflammatory strength gives CBG clinical applications in cases of glaucoma and Crohn’s disease. As in the case of several cannabinoids, CBG may promote bone growth and displays antitumour activity by negatively affecting metastasizing cells. CBG shows cytotoxic activity on human epithelial cell carcinoma, and is the second-most effect cannabinoid at treating breast cancer.

CBGA is an unstable molecule and is very likely to undergo transformation. Through one of three possible cyclization reactions, CBGA may form ∆9-tetrahydrocannabinolic acid (THCA). THCA is generally the most abundant cannabinoid found in cannabis and easily decarboxylates under heat to form THC. The plant synthesizes THCA as a protective mechanism for the plant against environmental factors such as UV damage, insect damage and microbial infection. THCA produces necrosis within the plant’s own tissues to promote healthy growth or avoid external stressors. The structure of the sticky THCA glands actually trap insects away from the plant’s surface. In the ECS, THCA is a cannabinoid receptor agonist without psychoactive effects. Its antimicrobial effects are also displayed in humans, as well as it being a potent antioxidant making it another neuroprotective cannabinoid. Like CBG, THCA may be used in antitumour applications by preventing cell proliferation. It is also an excellent analgesic and anti-inflammatory. THCA shows promise in treatment of epilepsy through antispasmodic capacity, and is used for its antiemetic effects to promote weight gain.

As previously stated, most THC is present in cannabis in its acid form. THC is the cannabinoid responsible for the ‘high’ created from consuming cannabis. THC is a partial agonist at both CB1 and CB2, thus it has an impressive range of biological effects and clinical applications. THC creates its psychoactive effects by improving sensory function and mental activity, altering spatiotemporal perception, and creating a sense of euphoria or mental wellbeing. Although the exact mechanism is not yet known, it is suspected that THC’s psychoactivity is related to its inhibitory effect on the cellular enzyme adenylate cyclase. THC ingestion brings an increase in creativity and sexual arousal. THC also functions mentally as an antidepressant and anxiolytic, can stimulate neurogenesis, and provides neuroprotection through strong antioxidant capability. THC is a potent analgesic and anti-inflammatory agent, and may be used clinically in treatment of asthma, pain, glaucoma, and Crohn’s disease. It also has antispasmodic use in treating epilepsy. THC will increase appetite through antiemetic and anticachexia effects, and can be used to treat wasting disorders in which are involved excessive weight and muscle loss. Finally, THC is an anticancer cannabinoid and may be used to prevent tumour growth.
Cannabinol (CBN) is formed as a byproduct of non-enzymatic THC oxidation, caused by heat or UV exposure. As such, it is found in higher concentrations in older cannabis plants. CBN is also psychoactive but has a much lesser affinity for CB1 and CB2 than THC and so has a lesser psychoactive potency. Like THC, CBN is an anxiolytic as well as an analgesic, anti-inflammatory agent, and antispasmodic agent. This combination of effects gives CBN value in treatment of Lou Gehrig’s disease. Like CBG, CBN is antimicrobial and effective against mRSA, and can be used to treat psoriasis by preventing keratinocyte proliferation. CBN is of interest in treatment of burns as it is an agonist of high-threshold thermosensor receptors. Finally, CBN may be used to prompt bone growth by stimulating recruitment of stem cells in bone marrow.

CBGA may undergo a different enzymatic cyclization to form cannabidiolic acid (CBDA), which then decarboxylates under heat to create its neutral form, cannabidiol (CBD). Like THC, most CBD in cannabis is present in its acid form, CBDA. CBD has long been considered the most medically-useful cannabinoid. It is the second most prevalent cannabinoid in cannabis drug chemotypes. Unlike THC, CBD is not sensitive to oxidation, and is not psychoactive. It has a lesser affinity for CB1 than THC does, making it a competitive antagonist to CB1 in the presence of THC; CBD will also inhibit uptake and hydrolysis of AEA in this manner. Therefore, CBD in the presence of THC will lessen the psychoactive effects of THC, but will delay its metabolization for longer. CBD has a greater affinity for CB2 than it does for CB1, accounting for its versatile pharmacological effects. CBD is a powerful analgesic, muscle relaxant, and antioxidant; its strength in these applications is greater than of any other cannabinoid. Its analgesic potency makes it a prime treatment in cases of fibromyalgia. As an anti-inflammatory agent, CBD is used to treat Crohn’s disease, multiple sclerosis, rheumatoid arthritis, and allergic reaction. CBD’s antispasmodic power gives it use as an anti-epilepsy medication. CBD is an antidepressant, antipsychotic and anxiolytic, which gives it a wide range of mental clinical applications including dampening tobacco cravings, lessening paranoia and anxiety, and insomnia relief. CBD is a strong antibacterial, and is the most effective cannabinoid against mRSA. CBD is used to help patients with Type II Diabetes manage their glucose intake, and is also effective in managing appetite with its antiemetic properties. It is an antiprokinetic agent of use in symptoms of diarrhea. CBD has a therapeutic role in cell migration disorders such as endometriosis or metastasizing cancers; its antitumour and antimetastatic properties have shown the most promise in fighting breast cancer. CBD protects the brain from neural degradation with its antioxidant strength, and is used clinically for prevention of stroke. It is also used therapeutically as an anti-ischemic medication. CBD inhibits production of sebocytes in small doses, and in larger doses produces apoptosis, which makes CBD an excellent anti-acne treatment.

CBGA can undergo a third type of enzymatic cyclization to form cannabichromenic acid, which will create cannabichromene (CBC) from heat decarboxylation. CBC does not directly bind CB1 or CB2 but rather indirectly activates the ECS by inhibiting degradation of the endocannabinoids AEA and 2-AG. Therefore, CBC itself is not psychoactive but can intensify the effects of THC when in its presence by delaying its degradation in the same way. CBC is a very strong antidepressant- it is up to ten times stronger than CBD in this regard. CBC is also used as an analgesic. CBC displays antimicrobial
and antifungal properties, and is used in anti-acne treatment as it reduces sebum production. Finally, CBC is of interest as an antiprosthetic, as it uniquely can reduce hypermotility in the gut without producing hypomotility; most available antidiarrhea medication carries the risk of producing constipation in turn.

CBGVA will react enzymatically to form tetrahydrocannabinaric acid (THCVA) which, like THCA, will undergo heat decarboxylation to form tetrahydrocannabinvarin (THCV). THCV is a CB1 agonist at low doses, but at higher doses works as a CB1 antagonist. It functions to increase the speed and intensity of THC’s effects. THCV is an analgesic but its effects as such are particularly effective in central nervous system conditions. Unlike any other known cannabinoid, THCV works to reduce appetite and is used clinically to encourage weight loss and decrease body fat. It also is used in this regard to help patients with Type II Diabetes manage their glucose intake.

There is evidence to show that the individual effects of each cannabinoid may not be as great as the synergistic effect of them combined. It has been shown that CBN administered in the presence of THC displays a synergistic anxiolytic effect greater than the effect of either CBN or THC alone. CBD administered with THC serves to provide the benefits of both cannabinoids without the anxiety and paranoia that may be associated with THC use. Not only may the cannabinoids display synergy between each other, it is shown that cannabinoids will work synergistically with other available cannabis compounds to produce an entourage effect.

CONCLUSION

Discovery of cannabinoids and how they function led to an understanding of the endocannabinoid system and its applications in health. Current research shows that the cannabis plant provides a valuable source of medical potential. There is value in use of the whole cannabis plant, as synergistic effects between the plant compounds can produce a more significant physiological effect on the human system. Phytocannabinoids may be used to stimulate creation of more endocannabinoids, strengthening the ECS before disease even occurs, and boosting the body’s natural strength. Phytocannabinoids provide a natural and more effective approach to many existing aggressive and dangerous medications. With an awareness of how phytocannabinoids interact with our endogenous ECS, cannabis may be grown and processed in a way to create a diverse range of medicinal products.

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