REVIEW ARTICLE

Therapeutic Potential of *Cannabis* Plant

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Abstract

The aim of this review article is to outline the role of the plant *Cannabis sativa* in treating human ailments. Giant pharmaceutical companies are marketing phytochemicals extracted from *Cannabis* plant and its derivatives to treat epilepsy and multiple sclerosis. The present review emphasizes cannabinoids – its derivatives and synthetic analogs – as an active pharmaceutical Ingredient to treat ailments related to autoimmune human body responses. The endocannabinoid system CB1 and CB2 respond differently to various phytochemicals such as cannabidiol, tetrahydrocannabinol and terpenes. They also interact with the endogenous ligands synthesized by the human body. The role of nanotechnology in the design of a drug delivery system is discussed in this review. The advantages with the use of Quantum dots are briefly outlined. *Cannabis*-based phytochemicals are known for psychotic and non-psychotic effects. We have underlined the immense potential of this plant in treating diseases. Cannabidiol (CBD) as one of the main non-psychotic phytochemicals, has established itself as an active pharmaceutical agent in some approved medicines worldwide. *Cannabis*-based phytochemicals can be used as targeted drug delivery vehicles. Future direction in this field could be a synthesis of derivatives of cannabidiol and its targeted drug delivery to the cannabinoid receptors. In the oral route, the terpenes give the wholesome experience of consuming *Cannabis*.

Keywords: Cannabinoids, Drug delivery, Endocannabinoid receptors, Nanotechnology, Quantum dots.

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Introduction

Cannabis sativa is an umbrella term for *Cannabis sativa*, *Cannabis indica* and *Cannabis nideralis*. They belong to the family Cannabaceae. It is commonly referred to as hemp, specifically hemp, which refers to the cultivation of *Cannabis* for non-drug use, namely textiles, biofuel, biodegradable plastics, and animal feed. In India and elsewhere, *Cannabis* is known as marijuana, pot, weed, bhang, and chillam (The Narcotic Drugs and Psychotropic Act, 1985). *Cannabis* belongs to the narcotic class of drugs and its use is illegal in many jurisdictions (Bewley-Taylor, 2013). Traditional use of *Cannabis* has found its existence in the world's oldest religions such as Hinduism and Judaism and cultures such as Greek and Roman for more than 5000 years. In these age-old traditions *Cannabis*-based products are offered to deities as part of the worship ritual (Butrica, 2008). At Maha Shivratri the festival of Lord Shiva, *Cannabis* (also known in India as Bhang) is distributed in temples as Prasad (food offering) (Godlaski, 2012). In India, the Narcotics drugs and Psychotropic Act passed in 1985 rules out "bhang" from the definition of *Cannabis*. The act in effect, allows the use of bhang during the traditional festival of Holi. Under this act, the production and sale of resin and flowers is prohibited while its leaves and stem are permitted for use especially for industrial and research purposes. *Cannabis* as a plant is valued not just for its recreational value but also for its medicinal value. Today *Cannabis* occupies an important place among medicinal plants. The term "medical marijuana" is gaining currency (Iversen, 2009; Ogbome *et al.*, 2000). GW Pharmaceuticals, a British pharmaceutical company has introduced *Cannabis*-based medicines such as Sativex and Epidiolex for multiple sclerosis and epileptic attacks in children, respectively. The phytochemicals in *Cannabis* are mainly the Cannabinoids and the terpenes. There are about 144 cannabinoids and over 100 terpenes in *Cannabis* plant that have been isolated so far (Lazarjani *et al*., 2020). The Cannabinoids are used in medicine while terpenes are responsible for the flavour and aroma of the plant. In the current trend the synergy between these is important to give the wholesome experience of using *Cannabis* as a medicine (Mechoulam *et al*., 2007). Among the Cannabinoids, the compound that affects our neuro-cognitive outcomes on consumption of *Cannabis* is none other than the cannabinoid: *Tetrahydrocannabinol* (THC). It was first isolated in 1964 by Gaoni and Mechoulam with the advent of modern separation techniques (Gaoni and Mechoulam, 1964). They not only established the structure of THC but also proved that the psychosomatic effect of *Cannabis* is due to THC. Mechoulam et al succeeded at the same time in elucidating the structure of *Cannabidiol (CBD)* although CBD was already discovered in 1930s. The psychoactive ingredient in *Cannabis* is THC while the non-psychoactive ingredient is CBD. Their chemical structures are given in Fig. 1 (*Cannabidiol | C21H30O2 | CID 644019 - PubChem*,) (*Dronabinol | C21H30O2 | CID 16078 - PubChem*)

The scientific interest in *Cannabis* really began with Rafael Mechoulam's discovery, separation, and elucidation of the structure of THC and the establishment of the fact that the intoxicating effects are due to THC. His group further went on to synthesize THC in a laboratory. The discovery of the endocannabinoid system in our body by Dr. Lumir Hanus in 1992 at the Hebrew University in Jerusalem marked the emergence of new class of constituents of *Cannabis* such as Phyto cannabinoids, terpenoids, flavonoids, and phytosterols. While the Phyto cannabinoid THC is associated with the

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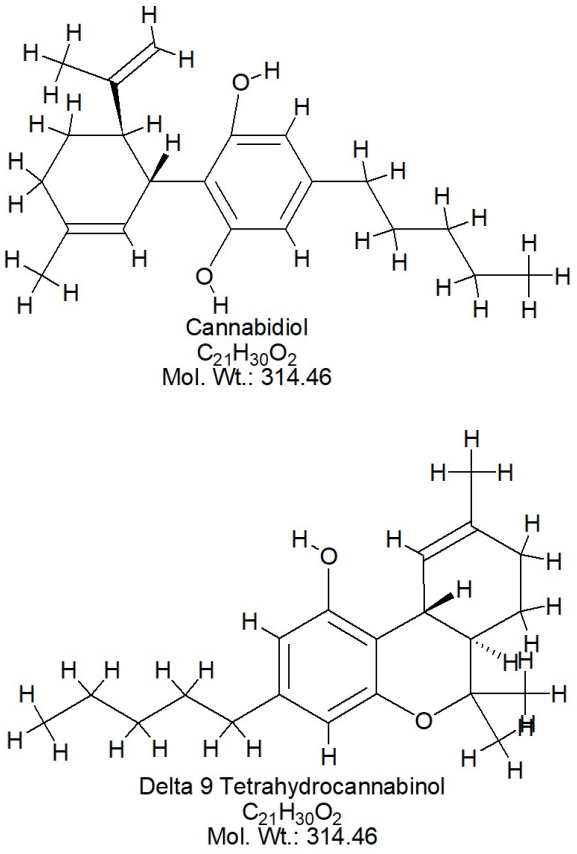

Fig. 1: Chemical Structures of Cannabidiol (CBD) and Tetrahydrocannabinol (THC)

recreational "high", the pandora box of *Cannabis* also reveals useful molecules such as cannabidiol (Maremmani *et al.*, 2004) (Nelson 2023). The medicinal properties of the plant can be attributed to CBD and its synthetic analogs (Burstein, 2015) The pharmaceutical properties of CBD include anti-inflammatory, antiemetic and anti-psychotic properties (Walker *et al.,* 2019). Clinical trials have shown that CBD suppresses the auto-immune reactions in Graft versus Host diseases (GvHD). An example is replacement of bone marrow in cancer patients who showed reduced autoimmune response on administration of CBD.

The father of *Cannabis* research - Prof. Rafael Mechoulam, believes that the future of Cannabinoids as pharmaceutical ingredients lies in the derivatives of CBD. Other subclasses of cannabinoids are: cannabigerols (CBG), cannabichromene (CBC), cannabidiol (CBD), cannabinol (CBN), cannabinodiol (CBDL), cannabicyclol (CBL), cannabielsoin (CBE) and cannabitriol (CBT). The class of synthetic cannabinoids is gaining importance because they serve two-fold use: as designer drugs (recreational drugs to replace the illegal natural analogues) and as drugs that can replace the natural cannabinoids for the purpose of research. Our body has CB1 and CB2 receptors distributed in some parts (Mackie, 2008). They form the endocannabinoid system, so named because they respond to Cannabinoids. It was thought to be inevitable that there would exist endogenous ligands that would bind to these receptors. Therefore, the next natural milestone in the field of *Cannabis* research was the discovery of these ligands called as endocannabinoids or the cannabinoids that are synthesized by the human body(Hanuš, 2007). Wrote the landmark paper on their discovery of anandamide, the first endogenous cannabinoid to be discovered (Devane *et al.*, 1992). After the identification of AEA (Devane *et al.*, 1992), another major endocannabinoid which was discovered was 2-arachidonoylglycerol (Sugiura *et al.*, 1995), and both compounds are still recognized as the two main members of an ever-growing family of bioactive lipids (Mechoulam *et al.*, 2014). The cannabinoid receptors are distributed throughout our body and are known to be disease specific (Hill *et al.*, 2012). As our understanding of these receptors improve, we appreciate that cannabinoids have an important role to play in curing diseases especially diseases that are autoimmune and inflammatory in nature (Compston and Coles, 2008). The medicinal value of *Cannabis* is a reality today with two drugs in the market: Epidiolex for treating epilepsy and Sativex (Giacoppo *et al.*, 2017) for treating multiple sclerosis (a neuro-inflammatory disease). Cannabinoid-based Biosensors and drug-delivery systems in an important phase of *Cannabis* research. The impact of Nanotechnology in the field of medicine is ever-evolving. In this review we discuss the developments involving nanoforms of cannabinoids and their potential applications as Biosensors. This review attempts to bring into focus the delivery of cannabinoids by nanotechnology which may involve surface modification of cannabinoid nanoparticles and the synthesis of their composites with well-characterized nanomaterials (Bouchard *et al.*, 2016; Brents, 2016). It is known that to obtain CBD in its purest form is a very difficult task due to the uncertainty of inexpensive extraction technique being employed while following the norms of good manufacturing practices (GMP) as set by the regulatory authorities to define the quality of the product (World Health Organization 2018) (WHO Geneva, 2018). Fig. 2 represents the challenges in the synthesis of pure CBD.

Even a trace impurity of THC can be a cause of worry for patients with respiratory and psychiatric disorders (Bouchard *et al.*, 2016; Geneva, 2018; Lewis *et al.*, 2017).

The Endocannabinoid System and the Endocannabinoids

The journey towards the discovery of the endocannaboid system (made up of endocannaboid receptors CB1 and CB2 and Endocannabinoids) started way back in 1895 with the discovery of Cannabinol (CBN), the very first phytochemical to be isolated from *Cannabis* by (Wood *et al.*, 1899). Cahn determined its structure in 1930. Wood obtained high boiling

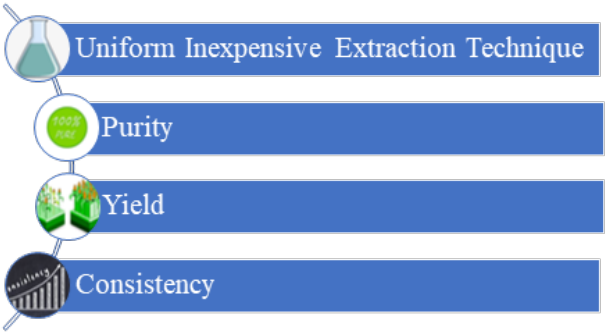

Fig. 2: Challenges in synthesis of cannabidiol

viscous oil which was amber-coloured. The Cambridge group carried out acetylation and called it cannabinol acetate. They hydrolyzed it to phenol and called it cannabinol. Of course, the red viscous oil was not homogeneous and so the preparation of cannabinol acetate in relatively high concentration led to the belief that cannabinol was the major component of *Cannabis* genus. Historically cannabinol is the first phytochemical to be isolated from *Cannabis* by (Wood *et al.*, 1899). It is known today that Woods must have worked on old samples of *Cannabis* plant wherein most of the THCA is oxidised to CBN. This reaction is shown in Fig. 3 In a fresh sample of *Cannabis*, CBN is present in trace amounts (*Cannabinol | C21H26O2 | CID 2543 - PubChem*; *delta9-Tetrahydrocannabinolic acid | C22H30O4 | CID 98523 - PubChem*)

Roger Adams from University of Illinois first isolated CBD in 1940 (Adams and Hunt, 1940). Without modern techniques, the CBD structure was not deciphered until in 1964; with the help of NMR spectroscopy, (Mechoulam and Shvo, 1963) succeeded in elucidating its structure. Yachiel Gaoni and Mechoulam also succeeded around that time in isolating THC as a neutral fraction from petroleum ether extract of *Cannabis* plant. A study on primates confirmed that THC caused catalepsy (induced state of trance) while CBD had no such effect. This conclusively established the fact that THC in *Cannabis* was responsible for the psychotic action while CBD was non-psychotic (Gaoni and Mechoulam, 19).

Chronologically and naturally, the discovery of the endocannabinoid receptors came after the path – breaking work of Rafael Mechoulam, namely the characterization of phytocannabinoids CBD and the discovery and characterization of THC derived from the genus *Cannabis*. Matsuda *et al* reported the existence of first cannabinoid receptor CB1 in 1990 through a discovery that an orphan G protein-coupled receptor (SKR6) derived from rat cerebral cortex influences and mediates the activity of THC in rat brain (Matsuda *et al.*, 1993). We now know that the phytocannabinoids exerted their effect on the human body through the endocannabinoid system made up of at least two receptors, namely the CB1 and CB2. The receptors were so named after their discovery in the numerological order.

The endocannabinoid system is present in all vertebrates, including birds, reptiles, amphibians, mammals, and fish. *N-arachidonoylethanolamine (anandamide; AEA) and 2-arachidonoylglycerol (2-AG)* has been the interest of researcher as they bind and activate two g-protein coupled receptor cannabinoid receptor 1 and cannabinoid receptor 2. Fig. 4 gives the structure of these endocannabinoids (*Anandamide | C22H37NO2 | CID 5281969 - PubChem*)(*2-Arachidonoylglycerol | C23H38O4 | CID 5282280 - PubChem*)(*Arachidonic Acid | C20H32O2 | CID 444899 - PubChem*).

The receptors are present throughout the body- skin, bone, fat tissue, pancreas, skeletal muscle, heart, liver, blood vessels, kidney, immune cells, and gastrointestinal tract. They are the most versatile receptors that affect our sensation of pain, memory, appetite, reproduction, and mood swings. The similarity in their structural proteins range between 40 to 70%. The CB1 Receptors are expressed mainly in the brain, the central nervous system, but also in the liver, lungs, and kidneys (Howlett *et al.,* 2010). The CB2 receptors are expressed in the immune

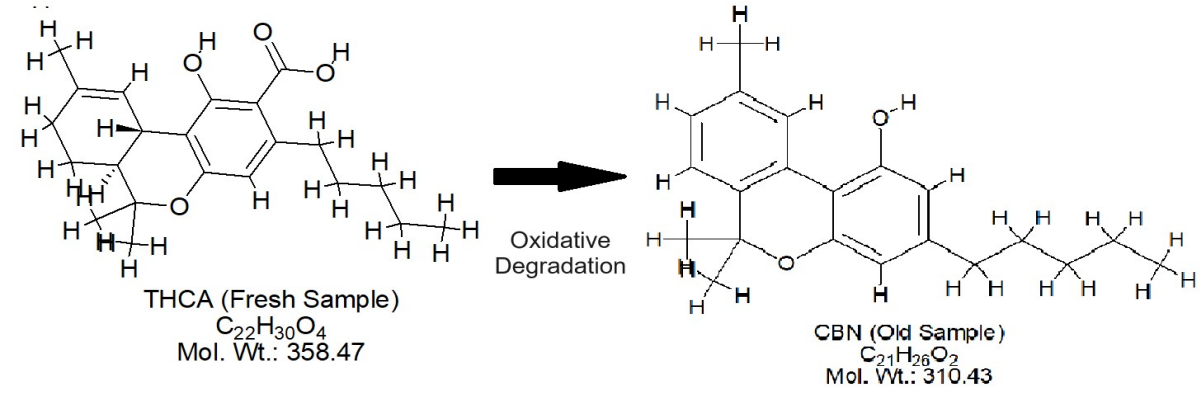

Fig. 3: Oxidative degradation of Tetrahydrocannabinolic acid (THCA) to Cannabinol (CBN)

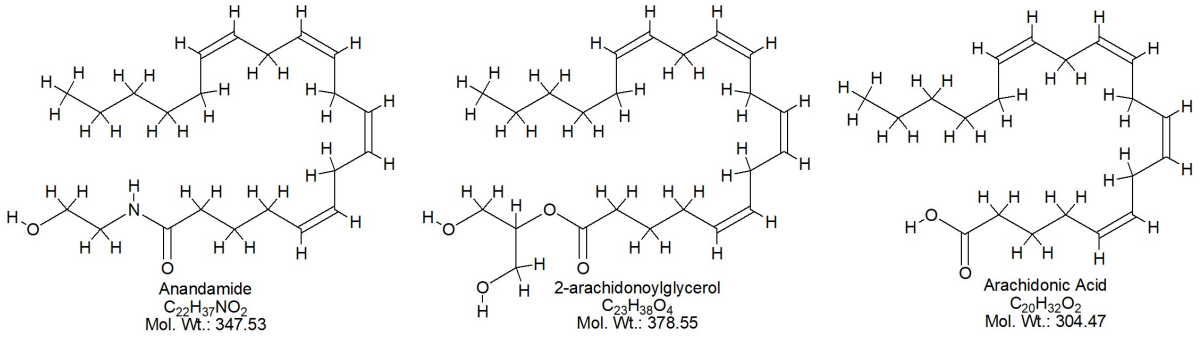

Fig. 4: Chemical Structures of the Endocannabinoids

cells such as lymphocytes and hematopoietic cells which form the part of peripheral nervous system. They belong to the family of seven-transmembrane G-protein coupled receptors (G_i/G_o proteins). The receptors can initiate signals in a manner which is typical of these proteins (Munro *et al*., 1993). They inhibit the activity of adenylyl cyclise, regulate the opening of K^+ channels, closing of Ca^{2+} channels and stimulate the activity of the protein-kinase enzyme (Bouaboula *et al*., 1996). Both the endocannabinoids are well characterized, highly lipophilic, and derivatives of Arachidonic acid.

Although these endocannabinoids are structurally different from THC, we continue to call the receptors as Endocannabinoid receptors because we are yet not sure if these *ecosanoid molecules* are the primary endogenous ligands/agonists. AEA and 2-AG are retrograde molecules because they belong to the category of retrograde messengers as they carry the signals of stress and environmental sensing to the nucleus of the cells and hence maintain metabolic homeostasis. More specifically, they are retrograde neurotransmitters where the retrograde signalling begins in postsynaptic neurons and is propagated to presynaptic neurons. Besides the endocannabinoid, nitric oxide is another very prevalent retrograde neurotransmitter. Anandamide and 2-AG are synthesized on demand. Once they are inside the cell they are hydrolysed to Arachidonic acid and ethanolamine by the enzyme FAAH (Fatty Acid Amide Hydrolase). Anandamide behaves like THC in being partial agonist for CB1 and CB2 receptors; its activity at CB2 receptors is even less than that at CB1 Receptors. 2-AG is an agonist at both CB1 and CB2 receptors and like anandamide has a relatively higher affinity for CB1 receptors than for CB2 receptors (Pacher *et al*., 2006). In rats whose genome CB receptors are deleted, called CB knock-out rats, showed response to anandamide proving that anandamide is not specific to CB receptors (Ross, 2003). It was established that anandamide in addition to CB receptors shows response to vanilloid receptors.

Cannabidiol (CBD) forms a major component of *Cannabis* plant- up to 40% of the plant's extract is non-psychotropic unlike THC which shows psychotropic effects (*Cannabidiol | C21H30O2 | CID 644019 - PubChem*, [s.d.]-c). The anti-inflammatory property of cannabinoid is attributed to it being antagonist of the CB1 and CB2 receptors (Nagarkatti *et al*., 2009). Cannabidiol is an anti-cannabinoid that prevents the endocannabinoids' activation of the receptors (McPartland *et al*., 2015). Cannabidiol does this indirectly because it has a very low affinity for the CB receptors itself. Cannabidiol binds equally to active and inactive CB receptor sites and is a neutral antagonist helping to maintain the metabolic homeostasis. For more understanding on the biosynthetic pathways of endocannabinoids see the reviews, (Ueda *et al*., 2013)(Fezza *et al*., 2014)(Maccarrone, 2017)(Battista *et al*., 2014).

Drugs based on cannabidiol

Ag-tetrahydrocannabinol is prone to oxidation. Prolonged contact with air results in the gradual oxidation of Ag-tetrahydrocannabinol to cannabinol (CBN). There are currently two oral formulations of Ag-tetrahydrocannabinol commercially available by prescription in the United States: Dronabinol, is available commercially as Marinol® TM soft gelatin capsules and Namisol® TM is available as sublingual tablets, have been approved by the Food and Drug Administration (FDA) for the control of nausea and vomiting associated with chemotherapy and for appetite stimulation in AIDS patients suffering from the wasting syndrome.

Marinol® TM is formulated by dissolving Ag-tetrahydrocannabinol in sesame oil to manufacture soft gelatine capsules suitable for oral administration. Marinol® gelatine capsules of Marinol® exhibit full therapeutic potency approximately one hour following their administration. Onset of therapeutic potency for Dronabinol is shorter, approximately 0.5 to 1 hour after oral administration, with a peak therapeutic effect lasting for a time of 2-4 hours post administration. However, the amount of Dronabinol reaching the blood stream by absorption through the digestive system is only 10-20% of the administered dose. Fasting or food deprivation may further decrease the rate of absorption of Dronabinol. On the other hand, Namisol® has a rapid uptake through the sublingual mucosa. However, the tablet must be kept under the tongue for the time it takes to dissolve and stimulates the flow of saliva. This make it difficult for patients to avoid swallowing the tablet when substantial amounts of saliva are produced. For instance, Nabilone is a synthetic cannabinoid marketed as Cesamet® in Canada the United States, the United Kingdom and Mexico. Nabilone is formulated as capsules suitable for oral administration. Cesamet® TM is approved for use as an antiemetic and analgesic for neuro pathic pain. Sativex®, is a mouth spray containing △-tetrahydrocannabinol (THC) and cannabidiol (CBD). It is approved for the treatment of spasticity due to multiple sclerosis. Administration of synthetic cannabinoid formulations show fewer undesirable side effects than THC. Because of their poor absorption and bioavailability, oral formulations have the additional disadvantage that they require several administrations a day, making it inconvenient for patients with difficulty swallowing. Accordingly, there is an urgent need in the art for oral formulations of cannabinoids with improved dissolution and taste and enhanced bioavailability and absorption, while at the same time do not cause gastrointestinal irritation.

Abnormal neuronal activity in the brain cortex leads to seizures giving rise to a condition of epilepsy. In children of one age or older, it is called as Lennox-Gestaut syndrome. A more severe, rare and genetic epilepsy is called Dravet syndrome. These epileptic disorders show a good response on administration of the drug Epidiolex approved by FDA. *Cannabis*-based drugs are gaining momentum and here we produce a short section of report by WHO; the report we believe is exhaustive with respect to the cannabidiol-based drugs but more importantly it justifies the increasing interest in phytocannabinoids and their synthetic analogues to overcome hitherto invincible ailments:

"Epidiolex® is a liquid oral formulation of pure plant-derived CBD. It is produced by GW Pharmaceuticals in the United Kingdom and has shown positive results in Phase 3 trials for Dravet and Lennox-Gastaut syndromes, which are both treatment-resistant seizure disorders. The published results related to this therapeutic application are covered in Section 9: Therapeutic Applications (Abu-Sawwa and Stehling, 2020).
Arvisol® is an oral tablet containing pure CBD. It has been developed by Echo Pharmaceuticals in the Netherlands and is intended to be registered for the treatment of various

neurological disorders, including schizophrenia and epilepsy. Arvisol® is still undergoing Phase I clinical trials and is not yet available as a medicinal product (*Cannabidiol as a Different Type of an Antipsychotic: Drug Delivery and Interaction Study - Full Text View - ClinicalTrials.gov*, *Echo Pharmaceuticals - Specialist in cannabinoid based medication*; Costa *et al*., 2021).

Zynerba® Pharmaceuticals is developing a CBD gel (ZYN002) that is designed for transdermal use. The target indications for ZYN002 are Fragile X syndrome, adult refractory focal epilepsy and encephalopathies that are developmental and epileptic in nature. This formulation is currently in open-label Phase 2 testing for Fragile X syndrome. Dosing recommendations are to begin at 50 mg/day with increases up to 250 mg/day (Berry-Kravis *et al*., 2022; Merrick *et al*., 2016).

Bionorica® (Germany) has developed a pure CBD product that is extracted from hemp plants through a multi-stage process into a crystalline powder (production completed by THC Pharm) (*Bionorica sells Cannabis business to Canopy Growth | Bionorica* 2023; *Canopy Growth Divests Pharmaceutical C3 Cannabinoid Compound Company - Canopy Growth, 2021*).

STI Pharmaceuticals (Essex, United Kingdom) has developed a crystalline powder of pure synthetic CBD with multiple doses. This product has been evaluated in a Phase II study for its effects on marijuana-induced subjective effects in an oral capsule formulation (200-800 mg) (Bloomfield *et al*., 2022). Additionally, STI has produced an aerosolized 20 formulation for inhalation that was assessed using an ad lib dosing design (400 ug/spray) for cigarette smoking. Finally, another study examined CBD dissolved in olive oil as an oral preparation for graft versus host disease (*STI Pharmaceuticals Cannabinoid Products, 2023*).

INSYS Pharmaceuticals (United States) has developed an oral solution of pure CBD. It is currently in Phase 2 trials for childhood absence seizures (20-40 mg) and in a Phase 3 trial as an adjunctive therapy in conjunction with vigabatrin for infantile spasm-type seizures. Phase 2 trials are currently registered for Prader-Willi syndrome, and there is open-label access testing for treatment-resistant seizure disorders. This product has also been in a human laboratory trial and evaluated for anxiety-like behavior at doses from 300-900 mg with negative findings (*INSYS Therapeutics Initiates Phase 3 Clinical Trial of*, [s.d.]-a; *INSYS Therapeutics Initiates Phase 3 Clinical Trial of*, [s.d.]-b; *INSYS Therapeutics Initiates Phase 3 Clinical Trial of Cannabidiol (CBD) Oral Solution for Treatment of Infantile Spasms, 2018*).

PhytoTech Therapeutics (Tel Aviv, Israel) is developing an oral formulation (PTL101) that contains purified CBD embedded in gelatin matrix pellets. Phase 1 testing has been conducted on this product (10 to 100 mg) and found that it had significantly greater bioavailability compared to a reference product containing CBD (see Sativex® below) (Mitelpunkt *et al*., 2019; *PHASE 2 CLINICAL TRIAL FOR TREATMENT OF PEDIATRIC EPILEPSY UNDERWAY*, 2017; *PhytoTech initiates Phase II trial of PTL101 to treat pediatric refractory epilepsy - Clinical Trials Arena*, 2017).

Ananda Scientific (Israel) is producing pure CBD for medicinal purposes and reports having their Phase 1 pharmacokinetics studies underway presently in Israel, with numerous other trials planned in Israel and China (ANANDA Scientific's Liquid StructureTM Cannabidiol (CBD) to Be Clinically Evaluated for Opioid Use Disorder | Business Wire, [s.d.]; ANANDA Scientific's Liquid Structure™ Cannabidiol (CBD) to be clinically evaluated for Opioid Use Disorder).

In 2015, the US Food and Drug Administration (FDA) granted GW Pharmaceuticals Fast Track designation for intravenous CBD to treat Neonatal Hypoxic-Ischemic Encephalopathy (NHIE). The European Commission also granted orphan designation (EU/3/15/1520) for cannabidiol to be used in the treatment of perinatal asphyxia. NHIE and Perinatal Asphyxia are forms of acute or sub-acute brain injury due to asphyxia caused during birth and resulting from deprivation of oxygen during birth (hypoxia). Currently, no other treatments are available for these conditions, but there is evidence of the effectiveness of cannabidiol in animal models.

Numerous CBD products, including purported medicinal products, such as pills and capsules for various diseases/symptoms, and lotions, oils, foods, drinks, shampoos, cosmetics, etc., are being manufactured and distributed without regulatory oversight and often with unverified contents. The U.S. Food and Drug Administration has issued two major warning letters to manufacturers for fraudulent medical claims (describing health benefits with no evidence) and fraudulent production claims (marketing products containing specified concentrations of CBD when testing demonstrates the absence of CBD). CBD Combination Products CBD is presently marketed in combination with THC in a 1:1 ratio (Sativex®), which GW Pharmaceuticals market in number of countries. This combination is sometimes referred to as nabiximols, a name given by the United States Adopted Names (USAN) Council." (*CANNABIDIOL (CBD) Critical Review Report Expert Committeeon Drug Dependence: Fortieth report, 2018*)

In view of these reports and a reality that indeed *Cannabis* can provide answers to some disorders has spurred a great amount of research which also includes the nanovariants of CBD (Grifoni *et al*., 2022).

Nanotechnology and Phytocannabinoids

Nanoforms of CBD include nanocarriers or drug-delivery systems which offer to address the drawbacks of traditional medicines. The innumerable therapeutic uses of CBD such as antibiotics, analgesic, appetite stimulators, anticonvulsants, diuretic, and expectorants can be fully exploited with targeted drug delivery to the concerned tissues. The targeted delivery may not only help with increased bioavailability but also help to reduce or avoid psychotropic action. Increased bioavailability also means reduced local toxicity. Presently the challenges involved with Cannabinoids are their low bioavailability especially through the oral route and their instability under acidic conditions. The low bioavailability of 8-12% stems from it extremely lipophilic nature. Only that much amount of the drug can be absorbed by the bloodstream and delivered to the target to produce any therapeutic effect (Rapin *et al*., 2021). Nanotechnology can provide innovative ways to deliver the drug with increased bioavailability and increased stability in acidic conditions. The delivery vehicles could be liposomes, polymeric nanoparticles, viral encapsulated nanoparticles, or micelles loaded with drug (Conte *et al*., 2017; Jović *et al*., 2020). (Jovie *et al*., 2020 and Conte *et al*., 2017) Fig. 5 gives schematic representation of these drug delivery vehicles (Harrison and Spada, 2018; Hussein and Youssry,

2018).

Liposomes are spherical, self-assembling closed colloidal structures composed of lipid bilayers. Essentially, they are spheres of phospholipids. The outer lipid bilayer surrounds a central aqueous space. The drug if hydrophilic is encapsulated either in the central aqueous layer or in the hydrophobic tails if it is hydrophobic. The liposomal formulations of the anthracycline's doxorubicin (Doxil, Myocet) and daunorubicin (Dauno, Xome) are approved for the treatment of metastatic breast cancer and AIDS-related Kaposi's sarcoma. The next generation of liposomal drugs may be immunoliposomes, which selectively deliver the drug to the desired sites of action. Liposomes can be functionalized by ligands that enable targeted entry and protect them from possible damage from, for instance, blood plasma proteins. The anticancer therapeutic proporties or in general, anti-tumor properties of phytocannabinoids such as CBD, THC and CBG is reported by some groups (Singh *et al.*, 2019; Trivedi *et al.*, 2020).

Use of water-soluble polymers wherein the drug of choice is chemically linked, is an important strategy in targeted drug delivery. The polymer molecules form self-assembled micelles above a threshold concentration. The drug is loaded in a hydrophobic core and the hydrophilic core prevents aggregation and help to bind to proteins. The loading of drug is via a chemical linkage but where there is absence of suitable chemical groups for linking, block copolymers with appropriate composition can be used. Physical encapsulation is a method of choice for highly hydrophobic drugs wherein the hydrophobic core is engineered to accommodate the drug. More the compatibility between the core and the drug more will be the solubilization of the drug. However the converse process of releasing the drug should not be delayed.The compatibility and the rate of biodegradation of the micelles guide the optimum rate of diffusion of the drug from the micelles. Such polymers must be biodegradable to avoid toxic build up and to enable smooth excretion by the kidneys. The kidneys easily remove the degradation of polymers into monomers which have relatively low molecular mass while kidneys cannot remove the micelles whose molecular mass is above this limit. The micelles should be thermodynamically stable and should be able to retain their micellar structure long enough to reach the target site. The micelles should also be kinetically stable and should not dissociate into monomers. An example of such a polymer is PEG (polyethylene glycol) (Su *et al.*, 2019).

Cannabinoids based therapeutic agents are expected to work through the process of homeostasis whereby the immune system self-regulates to adjust its response to adaptive levels. In doing so, the immune response is attenuated, prevented, or induced. An example of homeostasis is the response of kidneys in the excretion of excess salts in case of high sodium uptake and sweating of the body to bring down the temperature to its core value of 37 C. Whenever a wound on the body is unattended for a long period, the body activates a chain of series of event for the individual to acknowledge its presence in the form of the pain. Our body has senses and emotions that help us to stay away from bad sites, odor, and heat. For example, people with an allergy to peanuts experience skin reactions. This is basically immunomodulation, where the body is reacting to hostilities or injuries. The Endocannabinoid system works through homeostasis and thus regulates our mood, sleep, appetite, memory, and reproduction. Immunomodulation by phytocannabinoids and synthetic cannabinoids has led to vast variety of pharmaceuticals as previously mentioned (Wright *et al.*, 2008)(Bloemendal *et al.*, 2020).

The toxicity of nano-formulation must be considered in terms of its ability to cross the blood-brain barrier, a semi-permeable membrane of endothelial cells that separates the blood from the cerebrospinal fluid. It acts as a barrier for pathogens, large hydrophilic molecules, antibodies, and signaling molecules belonging to the peripheral nervous system. The barrier allows the passage of small and hydrophobic molecules such as Oxygen and Carbon dioxide while the passage of large molecules such as RNA proteins assist glucose. Undoubtedly, the nanoforms must be large enough to not be able to cross this barrier. Toxicity concerns are addressed by analyzing the in vivo studies which include stability of the nanocarriers, its mechanic degradation, and its effect on the other organs of the body. A predominant mechanism causing toxicity is the disturbance in the cycle of ROS: Reactive oxygen Species. ROS cause cell death by injuring

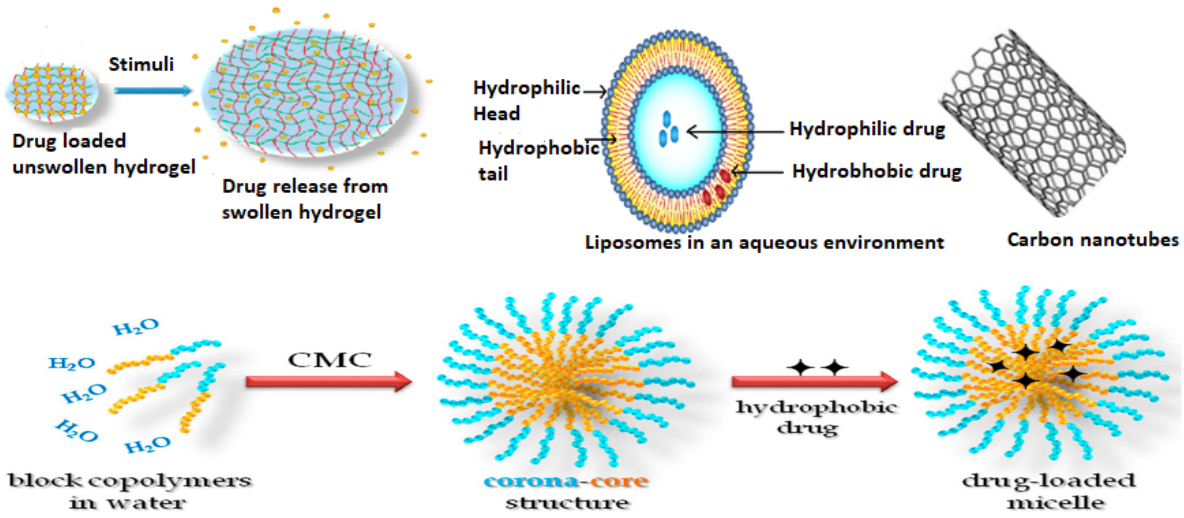

Fig. 5: Schematic representation of the drug delivery vehicles

biomolecules such as lipids in cell membranes, proteins, and nucleic acids. ROS is naturally generated by cellular respiration. The most prone organs are brain and lungs. The human body can neutralize these ROS through endogenous enzymes and non-enzymatic antioxidants by mitochondrial activity. The ability of nanomaterials when used in drug delivery systems, to disrupt this cycle, causing cellular damage and eventual organ failure must be taken into consideration. From the point of view of safety of these nanomaterials, one must also focus on the ability of these nanoforms to escape detection by the Reticuloendothelial system. The RES system comprises reticular and endothelial cells that are predominant in blood marrow, spleen, liver, and lymphatic nodes. These cells remove abnormal tissues, dead cells and in general substances that are foreign to human body. One way could be to disallow the adsorption of proteins on the surface of nanomaterials. Electrostatic forces and hydrophobic interactions facilitate the adsorption. The nanomaterials can be surrounded or embedded in hydrophilic polymers such as dextrans or PEG. Another way that the nanomaterials could escape the RES is by size reduction to quantum dots. This way they minimize the contact with serum proteins of the blood. Quantum dots of the order of 5 to 10 nm are very efficient in escaping the RES. Some examples are metal nanoforms (Li *et al*., 2016) and carbon-based composites (Jović *et al*., 2020). Nanoforms of CBD have shown immense potential to improve fertility rate in vivo (Bajilan, 2017; Hou and Zhu, 2017). Clinical trials must take into consideration the toxicity effects (Chen *et al*., 2019; Guan *et al*., 2020; Hardman, 2006; Klostranec and Chan, 2006; Missaoui *et al*., 2018; Skorupska and Grabowska-Jadach, 2019; Wang *et al*., 2013). Quantum dots could be the next level pursuit of scientific findings if explored with its conjugation to the extremes of quantum biology, quantum chemistry and quantum physics (Drbohlavova *et al*., 2009; Riviere, 2009; Zhao *et al*., 2017).

The interaction of phytocannabinoids with biomolecules could form a basis for construction of Biosensors. In one of the reports, binding between herring-sperm DNA and Cannabinol is monitored with Acridine orange as Fluorescence probe and using UV-visible and fluorescence spectroscopy. Effect of cationic proteins on gold nanoparticles-Aptamer Essays is another method for basis of construction of Biosensor. Biosensors based on aggregation of gold nanoparticles employing small molecules such as CBD and CBN is possible (Kang *et al*., 2015; Kara and Ertaş, 2017; Pawar *et al*., 2018; Rizvi *et al*., 2010; Rosenthal *et al*., 2011).

Quantum dots are nanocrystals with bulk exciton Bohr radius in the range of 2–10 nm. In contrast to bulk materials, Quantum dots have broad absorption spectra and narrow emission spectra. Their optical properties, namely the fluorescence characteristics can be tuned from the ultraviolet to the visible and near-infrared (NIR) wavelengths. This tunability is achieved by varying their surface chemistry and particle size. This fluorescence allows them to be used as fluorescent labels in drug delivery systems to monitor the metabolic process of the drug in the human body. Varying the surface chemistry also allows the quantum dots to be biocompatible, water soluble and non-toxic in nature. Paclitaxel forms a drug delivery system with CdTe@ CdS@ZnS quantum dots and serves as a drug of choice in treating and diagnosing various human cancers (Olerile *et al*., 2017). Glycine–proline–glutamate-conjugated graphene quantum dots (GQDGs) were investigated for the treatment of Alzheimer's disease and were found to have an inhibitory effect on the aggregation of amyloid-βfibrils (Xiao *et al*., 2016).

Conclusion

Cannabis-based phytochemicals are known for psychotic and non-psychotic effects. *Cannabis sativa* is rich in THC content while *Cannabis* indica is rich in CBD content. We have underlined the immense potential of this plant in treating diseases. This potential is based on the pharmaceutical properties of anti-inflammatory, antiemetic and anti-psychotic effects on the human body. As one of the main non-psychotic phytochemicals, CBD has established itself as the active pharmaceutical agent in some of the approved medicines used worldwide. It has the potential to form composites with nanomaterials and its induced effects on CB2 receptors, which is vital in treating diseases such as fertility disorders and auto-immune responses. As our understanding of the endocannabinoid system and cell signal transduction pathways grows so does the potential of *Cannabis*-based phytochemicals to be used as targeted drug delivery vehicles. Surface functionalization of Quantum dots is necessary for increasing water solubility, rendering bioconjugation (since reactions are all water-based), targeted drug delivery, and reducing toxicity. Such functionalization should survive the endosomal encapsulation and should be amenable to renal filtration and urinary excretions.

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Authors Contribution

Mr. Siddhesh Pote collected data and managed references using Mendeley. Dr Parul Khurana was involved with conception and design of the review. Dr Gaganjyot Kaur contributed to the analysis of the data collected. Dr Sonali Kokane organised and prepared the manuscript.

Conflict of Interest

None

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