Healthcare Technology Centre (HTC) Accelerate & Hemp Heros: Potential for Application of CBD-based Products in Health, Well-being, and Disease Treatments

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Contents

Direction for the Report

The purpose of this paper is to outline the potential use of Cannabidiol (CBD)-based supplement products and their ingredients as a novel preventative and treatment agent against. It is noteworthy that both delta-9 tetrahydrocannabinol (∆9-THC, or THC) and Cannabidiol (CBD) are frequently reference throughout the existing literature and this report, the focus is predominantly on CBD, the non-psychoactive cannabis plant extract. In alignment with a drive towards disease prevention- not cure- we take a look at the landscape surrounding the growing global acceptance of CBD product use in support of physical and mental health and well-being. We outline the origins of traditional CBD use and its integration into the world of legalised commercial products supporting consumers through mental and physical health and wellbeing challenges. We investigate the biosynthesis of cannabidiol, and its natural and synthetic analogues, to highlight the diversity and complexity surrounding the development from seeds- to-plants which are ultimately harvested to extract ingredients for use in everyday CBD products. There is a growing support for investigation of effects of cannabis plant-derived molecules in enhancement in quality of life, disease prevention and treatment, as well as symptom-mitigation across an array of disease areas. Through exploration of clinical and pre-clinical studies, we aim to consolidate current consensus on the novel therapeutic value of CBD products in disease areas including neurodegenerative disorders and cancers. Through this process we aim to identify the current landscape and identify avenues for future collaborative study in an area which focuses on health, wellbeing and quality of life improvement.

Introduction

Cannabis is a genus of flowering plants in the family Cannabaceae. There are currently disputes over the number of species within the genus. There are three species which are universally recognised. These three species are *Cannabis sativa, Cannabis indica*, and *Cannabis ruderalis* (Guy, Whittle, & Robson, 2004). There is some dispute over the whether these are subspecies under single umbrella species or are each individual species (GRIN Taxonomy, n.d.; The Leaf Online, 2015; United States Department of Agriculture, 2017). The plant is also commonly known as hemp and has been used historically used for multiple purposes including hemp fibre, hemp seeds, oils and juice; as well as for medicinal purposes, and as a recreational drug use. It is widely accepted that the genus of the species is indigenous to and originated from Central and upper South Asia (Gardens, 2019; Mahmoud, 2007). It is noteworthy that entheogenic use of cannabis dates to as far as 1500-2000 B.C.E. (Before Current Era); and there is evidence to suggest use of cannabis in religious and spiritual ceremonies earlier still (Sayin, 2014; Souza, Albuquerque, Monteiro, & Amorim, 2008). It is clear that cannabis has been used for medicinal and therapeutic purposes for some time, with other evidence of its use more than 5,000 years ago in what is now Romania (Bennett, 2010) and 10,000 years ago in Japan (Clarke & Merlin, 2013)

In the 1840s, the first investigators attempted to obtain an active extract from the leaves and flowers of hemp (Pharmacie, 1840). In later years, an ethanol extraction process was described that on evaporation of the solvent a dark resin, which he named cannabin (Kogan & Mechoulam, 2007). The chemical research on the plant cannabinoids and their derivatives have been actively investigated for over nearly two centuries (Mechoulam & Hanuš, 2000) It was in 1964 that ∆9-tetrahydrocannabinol (∆9-THC, more commonly known as 'THC'), the major psychoactive component of Cannabis, was isolated in its pure form by Gaoni and Mechoulam (Gaoni & Mechoulam, 1964). Following this breakthrough, THC became widely available and research outputs defining the newly isolated chemicals were published. The chemical advances in these publications described ∆9-THC, as well as on cannabidiol (commonly referred to as CBD), a non-psychoactive plant cannabinoid (Farnsworth, 1977). However, during the 1930s and 1940s growing concerns about the potential dangers of cannabis-based constituents abuse led to a ban for its medicinal use in United States and many other countries. Decades later cannabinoids are becoming considered again as compounds of therapeutic value, even-though its uses are highly restricted (Kogan & Mechoulam, 2007). It now appears that we are in the midst of a step-change towards the legalisation of Cannabis for medicinal research and recreational uses.

In 2013, in excess of 60,000 kilograms of cannabis was produced legally worldwide (INCB, 2014) and in 2014 to meet the demand of an estimated 182.5 million cannabis users [aged 15–64] (Crime, 2016). In order to meet the UN Narcotics Convention, a portion of cannabis strains have been bred to produce minimal levels of tetrahydrocannabinol (THC), the principal psychoactive constituent of the plant. Conversely, some strains are selectively bred to produce a maximum of THC. There is an array of compounds which are isolated or extracted from the plant to create products for medicinal and recreational use including balms, hashish and oils (Erowid, 2007). Following the establishment of the 2018 Farm Bill in the United States of America, "Industrial Hemp" was classified by the federal government as cannabis containing no more than 0.3% THC by dry weight (Legal Information Institute, 2018). This classification was also spanned to include hemp-sourced extracts, cannabinoids, and derivatives in the definition of hemp.

*"**The term "industrial hemp" means the plant Cannabis sativa L. and any part of such plant, whether growing or not, with a delta-9 tetrahydrocannabinol concentration of not more than 0.3 percent on a dry weight basis"***

7 U.S. Code § 5940.Legitimacy of industrial hemp research

Recent years has seen an increased interest in Cannabidiol (CBD), one of the hundreds of active ingredients in cannabis, for use in medicinal and recreational purposes. CBD is not to be confused with tetrahydrocannabinol (THC), the psychoactive component of the cannabis plant, or hemp, which exerts a feeling of 'high' to the consumer. With respect to legality and use of cannabis for recreational and medicinal use, the global landscape remains highly complex due to the variation of regulatory and governance processes practised in countries and territories. Supplementary ***Table 1- Legality of recreational and medicinal uses of Cannabis*** provides an overview of legal status of recreational and medicinal cannabis use by country and territory. The easing of restriction over the last decade has opened doors to research on the potential beneficial effects of CBD.

Recent interest in research on the uses of CBD includes its potential to tackle health conditions including pain syndromes(Hill, Palastro, Johnson, & Ditre, 2017; Ware et al., 2010) to insomnia, anxiety, and rare forms of childhood epilepsy syndromes (Thomas & Cunningham, 2018) such as Lennox-Gastaut syndrome (LGS) (Lattanzi, Brigo, Cagnetti, Trinka, & Silvestrini, 2018); as well as improvements in overall well-being. And as such, CBD is viewed as an alternative to, and a complementary remedy for, synthetic pharmaceutical medications. Use of cannabis, and its constituent ingredients, is contested on both sides. Part of this uncertainty stems from requirement to develop a robust evidence base to prove and support claims of improved clinical outcomes, or not. Upon initial review of literature, there is clearly a demand for further research to investigate which component(s) of the cannabis plant induce improvement the perceived improvement in patient outcomes (Ware et al., 2010); and extrapolate these findings to potential treatment of defined disease areas. To this end, we aim to highlight specific areas of progress in this report. We will also highlight research conducted in the veterinary space which support the use of CBD-based products for alleviating chronic conditions in pets.

Global demand for CBD products had increased significantly and continues to grow. The global CBD market was valued at USD 4.6 billion in 2018 and is expected to grow at a compound annual growth rate (CAGR) of 22.2% from 2019 to 2025 (B2B & B2C, 2020). Representing a large economic opportunity for organisations in this market.

In the next sections of this report we will outline the development of the cannabis plant and the underpinning molecular mechanisms of CBD.

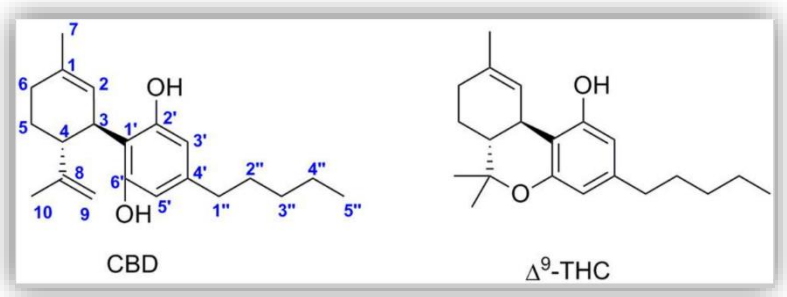


Figure 1: *Chemical Structures of Cannabidiol (CBD) and (–)-trans-Δ^9–tetrahydrocannabinol (Δ^9–THC). Modified from* (Morales, Reggio, & Jagerovic, 2017)

Cannabis Seed to Plant

Content of the following section is adapted from : https://www.leafly.com/news/growing/marijuana-plant-growth-stages

Cannabis plants go through a series of stages as they grow and mature. In this section we will briefly outline the process development of a cannabis seed to a plant. During cultivation, it is important to understand the growth requirements for each stage of the plant's life cycle, as each stage of growth requires varying conditions and care regimes. The requirements include variations in light, nutrients and water. The typical time taken to grow a cannabis plant from seed to mature plant for harvesting can be in the region of 14-32 weeks (4.5-8 months). The variability in time is largely due to variation in cultivation conditions- these conditions can also impact the extent of flowing, and the time required to reach this point in a vegetative cycle. The life cycle of cannabis can be broken down into four main stages from seed to harvest. The life cycle stages of a cannabis plant are (1) Germination, (2) Seedling, (3) Vegetative, and (4) Flowering - brief details of the growth stages are highlighted below.

(1) **Germination Stage.** Germination is the first stage of life for the plant and it begins with the seed. At this point, the cannabis plant is dormant. The seed is hard and dry to the feel and is light- to dark-brown in colour. Germination stage is typically in the range of 5-10 days and requires an 18hr light cycle. Once your seed has popped, it can be placed in its growing medium.

(2) **Seedling Stage.** At this stage the plant becomes a seedling. Development of traditional shaped cannabis leaves will begin to occur. Preliminary growth usually results in leaves with only one ridged blade. Once new growth develops, the leaves will develop more blades (1, 3, 5, 7, etc.). A mature plant can between 5-7 blades per leaf. This can vary depending on conditions. Particular care must be taken at this stage as the plant is at its most vulnerable. Considerations should include monitoring of excessive moisture and maintenance of a clean growing environment to mitigate against excessive watering, mould and disease. The seedling stage is in the range of 2-3 weeks and typically requires an 18hr light cycle.

(3) **Vegetative Stage.** There is an acceleration in growth during the vegetative stage. Spacing between the nodes can represent the type of cannabis you are growing. *C. indica* plants tend to be short and dense, while *C. sativas* grow tall and exhibit a more open foliage. This stage can be in the range of 3-16 weeks and typically requires an 18hr light cycle.

(4) **Flowering.** The flowering stage is the final stage of growth for a cannabis plant. Flowering occurs naturally when the plant receives less than 12 hours of light. Outdoors this occurs towards fall as the daylight shortens, or as the indoor light cycle is shortened. It is towards the end of stage that resinous buds develop (6-7 weeks). The flowering stage can be in the range of 8-11 weeks and typically requires 12hr light cycle.

CBD/CBDA Biosynthesis

As previously described *Cannabis sativa* L. (C. sativa or hemp) has been cultivated for at least 10,000 years and is one of the oldest cultivated plants (Schultes, Plowman, & Lockwood, 1974) and belongs to the small family of Cannabaceae. In the natural environment Cannabis is an annual, wind-pollinated herb, with both male and female flowers growing on separate plants. Broadly, the cannabis plant is known for the biosynthesis of cannabinoids, the terpenophenolic constituents that show psychoactive effects. Phytocannabinoid biosynthesis in cannabis plant also generates a number of secondary metabolites that interact with the human cannabinoid receptors. As a result of this, a new definition had to be made- phytocannabinoids. Phytocannabinoids are now defined as any plant-derived natural compound that can act as a ligand to human CB1 and CB2 cannabinoid receptors or share chemical similarity with cannabinoids (Gertsch, Pertwee, & Di Marzo, 2010). The CB_1 and CB_2 receptors both belong to the Class A family of G protein-coupled receptors (GPCRs) (Reggio, 2010). Intracellular signalling pathways of cannabinoid receptors is covered in the a following section (*see: CBD potential in prevention and treatments of Central Nervous System disorders and diseases)*. All parts of the *Cannabis* plant, except for seeds, can contain cannabinoids, but they mainly accumulate in the glandular trichomes of female flowers (Gagne et al., 2012; van Bakel et al., 2011).

The central precursor of the biosynthesis of phytocannabinoids in cannabis is the molecule Cannabigerolic acid (3-geranyl olivetolate or CBGA). Although there are a range of metabolites in the phytocannabinoid biosynthesis pathway, only three enzymes are involved in the biosynthesis of phytocannabinoids in the cannabis plant. These enzymes are Tetrahydrocannabinolic acid synthase (THCAS), Cannabidiolic acid synthase (CBDAS) and Cannabichromenic acid synthase (CBCAS) (Degenhardt, Stehle, & Kayser, 2017). There are over 60 additional naturally occurring cannabinoids which result from nonenzymatic modification (Degenhardt et al., 2017). See (Degenhardt et al., 2017) for comprehensive pathway of CBD/CBDA Biosynthesis: Chapter 2 of The Biosynthesis of Cannabinoids- available online.

Despite the identifications of CBD metabolites and naturally occurring analogs, there has been relatively scarcity of research and investigation into their pharmacological properties. Moreover, there is a area of research developing around synthetic CBD-based compounds. This interest is the result of several synthetic compounds showing interesting pharmacological properties- none of which, to the best of our knowledge upon time of writing, have been introduced into clinical trials. Naturally occurring CBD has an affinity to binding CB_1 and CB_2 cannabinoid receptors; however, the synthetic analogues (+)-CBD derivatives do bind to CB_1 and/or CB_2 receptors bind to one or both CB_1 and/or CB_2 receptors. Other synthetic analogues, such as Abn-CBD, O-1602, CBG, cannabimovone, ferruginene C, (-)-CBDV, and (-)-CBDA, have shown activity at other receptors including TPRV1, GPR35 and/or GPR18 receptors, or inflammation modulating enzymes such as COX-2 (Morales et al., 2017).

Endocannabinoid System (ECS)

The endocannabinoid system (ECS) is a biological system composed of endocannabinoids, which are endogenous lipid-based retrograde neurotransmitters that bind to cannabinoid receptors (CBRs), and cannabinoid receptor proteins that are expressed throughout the vertebrate central nervous system (including the brain) and peripheral nervous system (H. Freitas, Ferreira, Trevenzoli, Oliveira, & de Melo Reis, 2017; H. R. Freitas et al., 2018). The endocannabinoid system is currently considered under preliminary research as knowledge

and expertise in the field develops with respect to understanding the role of the system in physiological and cognitive processes. Research on the endocannabinoid system is currently being undertaken in a range of areas including, but not limited to pregnancy and fertility (Klein, Hill, Chang, Hillard, & Gorzalka, 2012; Wang, Xie, & Dey, 2006) pre- and post-natal development (H. R. Freitas et al., 2019; Fride, 2004), modulation of the immune system (Pandey, Mousawy, Nagarkatti, & Nagarkatti, 2009); and identification of pharmacological targets for pain management, mood modulation and anxiety alleviation (Aizpurua-Olaizola et al., 2017; Donvito et al., 2018).

Regulations on Hemp and CBD

Historically, Industrial hemp has been cultivated for its fibre for use in clothing, paper and construction. More recently, in part due to a better understanding of its safety and therapeutic properties, industrial hemp is grown to make CBD for use in food, food supplements and vape products. CBD is legal in the UK, however, UK laws and regulations surrounding the compound are complex. In this section of the report we focus on examples of CBD and hemp-based products which have been approved as novel foods and medicinal uses. But to begin we outline the current (at time of writing) regulations on Hemp and CBD.

Ireland

In Ireland CBD products are legal to sell as a food supplement once they are below 0.2% THC which is the EU limit. CBD oil is a regarded as a food supplement and not a medical product. In Ireland we have a licence to grow Hemp from the (Health Products Regulatory Authority) HPRA and Minister for Health. Our licence allows us to grow Industrial Hemp from a select list of EU approved hemp varieties which contain less than 0.2% THC and as a result are non-psychoactive.

United Kingdom

Cannabidiol (CBD) is not a controlled substance in the UK and is legal to possess and sell. CBD to be legal in the UK it must have a THC content of no more than 0.2%. To sell CBD oil you either need to be a licenced medical distributor or sell the product as a nutritional supplement. All our products are sold as food (Nutritional supplements).

Germany

CBD products below 0.2% THC are legal to sell and buy in Germany. Overall, Germany is one of the most progressive nations on the topic of Hemp and Cannabis.

USA

CBD and Hemp is legal in the United states due to Farm Bill being signed into law in 2018. The Farm Bill (Agriculture Improvement Act) legalized CBD that is derived from hemp and contains no more than 0.3% THC (by dry weight). All CBD products below 0.3% are legal in all States and sold as food supplements.

Novel foods Act

Novel foods are foods which have not been widely consumed by people in the UK or EU before May 1997. This means that the foods don't have a 'history of consumption. CBD was placed on the Novel Foods Catalogue in January of last year, meaning that the ingredient requires pre-market authorisation.

This is due to how CBD is extracted from Industrial Hemp making it novel. Most CBD is extracted using supercritical Co2 (Similar to decaffeinated coffee) or Ethanol extraction.

How we make our products does not fall into Novel Foods as we use Cold Press Technology which has been around and used prior to 1997. This means our products do not require a novel foods application and are also solvent free.

The CBD-based products in the market and as pharmaceuticals

Approved Cannabis-based Pharmaceuticals

To date CBD-based medicines are currently approved for alleviation of symptoms associated will multiple complex diseases. The UK National Health Service (NHS) provide prescriptions to CBD-based medicines in only a number of cases when no other treatment is suitable alternative options remain ineffective. These include children and adults suffering rare, severe forms of epilepsy; adults suffering with side effects of chemotherapy such as nausea and vomiting, and for Multiple Sclerosis (MS) patients suffering with muscle stiffness and spasms. In the UK approved CBD-based pharmaceuticals, regionally termed 'Medicinal Cannabis', include Epidiolex®, Nabilone (Cesamet®) and Nabiximols (Sativex).

On June 25, 2018 Epidiolex® was approved for treatment by US Food and Drugs Administration (FDA) for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome in patients two years of age or older. Epidolex was the first prescription pharmaceutical formulation of highly purified, plant-derived cannabidiol (CBD), a cannabinoid lacking the high associated with marijuana, and the first in a new category of anti-epileptic drugs (Devinsky et al., 2017, 2018; Thiele et al., 2018). In a double-blind, placebo-controlled trial, randomly assigned children and young adults (n=120) patients with the Dravet syndrome, a complex form of childhood epilepsy disorder, it was shown that cannabidiol resulted in a greater reduction in convulsive-seizure frequency than placebo and was associated with higher rates of adverse events (Devinsky et al., 2017). Following this another double-blind, placebo-controlled trial conducted across 30 clinical centres, with Lennox–Gastaut syndrome patients, a rare, severe form of epileptic encephalopathy, which frequently treatment resistant to available medications. Candidates in the age range, 2 to 55 years who suffer from two or more drop seizures per week were selected for trial. The study concluded that the addition of cannabidiol at a dose of 10 mg or 20 mg per kilogram per day to a conventional antiepileptic regimen resulted in greater reductions in the frequency of drop seizures than placebo(Devinsky et al., 2018). However, it was noted that adverse events with cannabidiol included elevated liver aminotransferase concentrations. Elevated levels of liver aminotransferase are typical symptomatic conditions of non-alcoholic fatty liver disease and alcoholic liver disease. An additional Phase III randomised, double-blind, placebo-controlled trial across 24 clinical sites in the USA, the Netherlands, and Poland showed that add-on cannabidiol is efficacious for the treatment of patients with drop seizures associated with Lennox-Gastaut syndrome and is generally well tolerated (Thiele et al., 2018). And as such a longer-term open-label safety trial was sought. The study also reported diarrhoea, somnolence, pyrexia, decreased appetite, and vomiting as the most common adverse events. Interestingly, the precise mechanisms by which EPIDIOLEX exerts its anticonvulsant effect in humans are unknown and does not appear to exert its anticonvulsant effects through interaction with cannabinoid receptors (GW Biosciences, 2018).

Nabilone (Cesamet®) is a synthetic cannabinoid for oral administration and is completely absorbed in the human gastrointestinal tract. Nabilone as a raw material occurs as a white to off-white polymorphic crystalline powder is used to treat severe nausea and vomiting caused by chemotherapy (U.S. Food and Drug Administration, 2006). Like other cannabinoids, has

complex effects on the central nervous system (CNS). It has been suggested that the antiemetic effect of nabilone is caused by interaction with the cannabinoid receptor system, i.e. the CB (1) receptor, which has been discovered in neural tissues. Cesamet was evaluated for its effectiveness and safety in the treatment of nausea and vomiting induced by cancer chemotherapy in patients receiving a wide variety of chemotherapy regimens, including lowdose cisplatin (20 mg/m2) in both placebo-controlled and active controlled (prochlorperazine) trials. During Cesamet treatment patients reported a higher incidence of adverse effects. The most frequent were drowsiness, vertigo, dry mouth and euphoria. However, most of the adverse effects occurring with Cesamet were of mild to moderate severity (U.S. Food and Drug Administration, 2006).

Nabiximols (Sativex®) is a herbal preparation containing a defined quantity of specific cannabinoids formulated for oromucosal spray administration with potential analgesic activity (resulting in pain relief without loss of consciousness). Nabiximols contains a standardized extract of tetrahydrocannabinol (THC), the non-psychoactive cannabinoid cannabidiol (CBD), other minor cannabinoids, flavonoids, and terpenes from two cannabis plant varieties. Cannabinoids interact with G protein-coupled cannabinoid 1 (CB1) receptors in the central nervous system, resulting in analgesic, euphoric, and anticonvulsive effects (National Center for Biotechnology Information, 2021). This oromucosal spray has shown to be an effective and well-tolerated treatment option for resistant MS spasticity (stiffening of muscles) in clinical practice (Flachenecker, Henze, & Zettl, 2014).

To date, it appears that much of the evidence suggesting cannabis could be an effective a medical treatment is anecdotal. Only in a few conditions have enough clinical trials been done to prove scientifically that the drug is safe and effective. Recent evidence shows that medicinal cannabis can have a therapeutic effect in a few specific conditions: chronic pain, nausea and vomiting caused as side effects of cancer therapies, and muscle spasticity symptoms in MS. To fill these gaps in our knowledge, a growing number of clinical trials are now taking place all over the world, looking at conditions such as childhood epilepsy, PTSD, and autism. This does not mean that cannabis or derivatives of cannabis are not effective in the treatment of other conditions, however more evidence on efficacy and mechanisms of action, and safety are required.

Another issue observed while reviewing clinical trials is that the trials are funded by the company that developed the drug. Thus, there is a financial interest tied to this drug being approved, which may have directed the primary and secondary outcome measurements to be focused on more positive effects. This can be supported through comparing studies lead by GW Pharmaceuticals to Dr. Leehley's at the University of Colorado, since Dr. Leehley's had examined more potential negative effects that GW did not include (Devinsky et al., 2017, 2018; Leehay, 2019). This is compounded by the vast exclusion criteria, and limited inclusion criteria on these studies, since patients that meet the excluded criteria may not necessarily be excluded from using the approved drug, which can be dangerous for public safety to generalize the safety of a drug based on data about a small homogeneous sample size. While these improvements would better the clinical trial process, the main aim of this review is to inform doctors, patients, and scientists of the clinical trials currently completed, and steer future trials to ensure the safety.

It is clear that Cannabis and cannabinoid drugs are widely used to treat disease or alleviate symptoms, but their efficacy for specific indications is not clear. This becomes clear in a study by *Whiting et al* in 2015 which explored a total of 79 trials (6462 participants) were included; 4 were judged at low risk of bias. Most trials showed improvement in symptoms associated with cannabinoids but these associations did not reach statistical significance in all trials.

Compared with placebo, cannabinoids were associated with a greater average number of patients showing a complete nausea and vomiting response (47% vs 20%; odds ratio [OR], 3.82 [95% CI, 1.55-9.42]; 3 trials), reduction in pain (37% vs 31%; OR, 1.41 [95% CI, 0.99-2.00]; 8 trials), a greater average reduction in numerical rating scale pain assessment (on a 0-10-point scale; weighted mean difference [WMD], −0.46 [95% CI, −0.80 to −0.11]; 6 trials), and average reduction in the Ashworth spasticity scale (WMD, −0.12 [95% CI, −0.24 to 0.01]; 5 trials). There was an increased risk of short-term AEs with cannabinoids, including serious AEs. Common AEs identified in these trials included events such as nausea, fatigue, dizziness, dry mouth, somnolence, euphoria, vomiting, disorientation, drowsiness, confusion, loss of balance, and hallucination. The main focus of this large literature-based study was on patient-relevant/disease-specific outcomes, activities of daily living, quality of life, global impression of change, and AEs. This particular systematic review of relevant clinical trials, which was conducted in circa 2015 by *Whiting, Wolff & Deshpande et al* aimed to review the evidence of the benefits and adverse events (AEs) of cannabinoids (Whiting et al., 2015). Included in this body of evidence was randomized clinical trials of cannabinoids. Review of these for the following indications: nausea and vomiting due to chemotherapy, appetite stimulation in HIV/AIDS, chronic pain, spasticity due to multiple sclerosis or paraplegia, depression, anxiety disorder, sleep disorder, psychosis, glaucoma, or Tourette syndrome. In summary there is moderate-quality evidence to support the use of cannabinoids for the treatment of chronic pain and spasticity. There was low-quality evidence suggesting that cannabinoids were associated with improvements in nausea and vomiting due to chemotherapy, weight gain in HIV infection, sleep disorders, and Tourette syndrome. Cannabinoids were associated with an increased risk of short-term AEs.

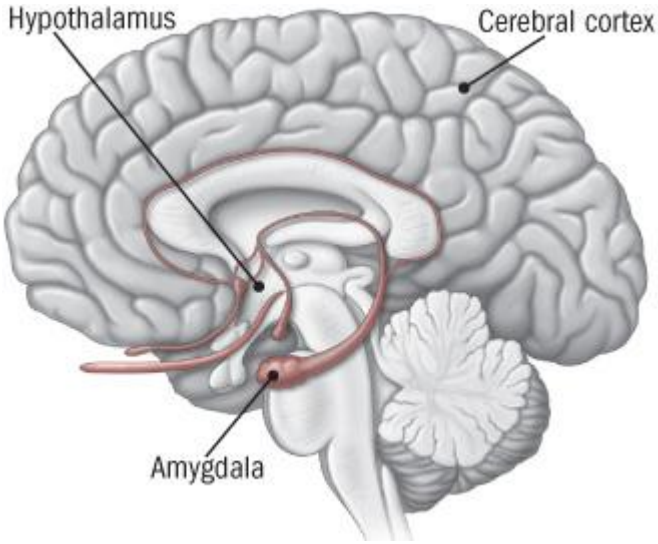
Quality of Life and Social Aspects

This next section summaries a section of the literature reviewed on stress, anxiety and sleep and role effects of CBD in these areas of quality of life.

Stress Response, Anxiety and Sleep

Part of the role of the amygdala is interpretation of the images and sounds. When it perceives danger, it transmits distress signal to the hypothalamus- which acts as the control centre of the brain. Upon experiencing a stressful event, the amygdala sends a distress signal to the hypothalamus. It is the role of the hypothalamus to communicate this signal with the rest of the body through the nervous system to take relevant action as a result of this stimulus (stressor). (Stephens, McCaul, & Wand, 2014). Secretion of glucocorticoids, a class of steroid hormone, as a result of a stress stimulus is a classic endocrine response (Whirledge & Cidlowski, 2010) with the ultimate purpose of self-preservation- often through triggering of the '*fight-or-flight'* response. This important hormonal response system is commonly known as the hypothalamic–pituitary–adrenal (HPA) axis. The axis is thought to be involved in stress stimulus signalling and release of stress hormones, glucocorticoids and primarily cortisol (Stephens & Wand, 2012). Persistent stress hormone secretion response to stress is considered harmful. Adverse effects of stress and how that impacts cognitive function depends on the type, timing, intensity, and duration of exposure (Sandi, 2013). Whilst in general, it is believed that mild stress facilitates an improvement in cognitive function, if the stress intensity passes beyond a predetermined threshold it causes cognitive disorders and impairs memory and judgment. This is believed to be as a result of stress on the hippocampus and prefrontal cortex. Other adverse physiological implications of stress include mediation of immune system through steroid receptor modulation (Blalock, Harbour-McMenamin, & Smith, 1985);

gastrointestinal (GI) implications such as loss of appetite, and loss of GI tract motility and digestive function; and impairment of reproductive function in males and females (Sandi, 2013; Whirledge & Cidlowski, 2010).



The endocannabinoid system has been implicated in the habituation of the HPA axis to repeated exposure to restraint stress. Current knowledge describes the role of endocannabinoid signalling as both a regulator of endocrine responses to stress and as an effector of glucocorticoid and corticotrophin-releasing hormone signalling in the brain (Hillard, Beatka, & Sarvaideo, 2016). Image (left) adopted from (Harvard Medical School, 2020)

Current literature has evidence showing that cannabinoid receptor 1 (CB1R) signalling can both inhibit and potentiate the activation of the hypothalamic-pituitary-adrenal axis by stress (Harvard Medical School, 2020). These contrasting effects also reveal the importance of the endocannabinoid system as a modulator and a regulating component of anxiety-dependent behaviour (Lutz, Marsicano, Maldonado, & Hillard, 2015). Moreover, Clinical findings suggest a negative correlation between endocannabinoid system activity and anxiety (Dlugos, Childs, Stuhr, Hillard, & de Wit, 2012).

Other result exploring the endocannabinoid system indicate a modulatory role with respect to anxiety, exploration, social behaviour. Results by Häring, Kaiser, Monory, & Lutz (2011) suggest that glutamatergic cannabinoid receptors are responsible for mediating aggression, but also produce an anxiolytic-like function by inhibiting excessive arousal. In this study excessive excitation produced anxiety in mice which limited the mice from exploring both animate and inanimate objects (Häring, Kaiser, Monory, & Lutz, 2011). In contrast, GABAergic neurons appear to control an anxiogenic-like function by limiting inhibitory transmitter release. Taken together, these two sets of neurons appear to help regulate the organism's overall sense of arousal during novel situations (Häring et al., 2011; Lutz et al., 2015).

Sleep

Pharmacological experiments have shown that the administration of endocannabinoids induce cannabimimetic effects, modulating sleep-wake cycles and sleep promotion (Murillo-Rodriguez et al., 2011). Thus, providing some evidence for the pharmacological potential of the endocannabinoid system on sleep modulation. There is evidence also in rats that intercerebroventricular administration of anandamide (ANA)- a brain lipid that binds to cannabinoid receptors with high affinity and mimics the psychoactive effects of plant-derived cannabinoid drugs- in rats decreases wakefulness and increase slow-wave sleep and REM sleep (Murillo-Rodríguez et al., 1998). Administration of anandamide into the basal forebrain of rats has also been shown to play a role in promoting sleep and suppressing arousal (Santucci, Storme, Soubrié, & Le Fur, 1996). Moreover, another study shows anandamide levels possess a circadian rhythm in the rat, with levels being higher in the light phase of the day, when rats are usually asleep or less active, since they are nocturnal. Suggesting that compounds like ANA which interact with the endocannabinoid system are likely to be accumulated in parenchymal tissues during the lights-off period (when animal is awake) and then, released into the CSF in order to reach target regions in turn to modulate diverse

behaviours, such as feeding and sleep (Murillo-Rodriguez, Désarnaud, & Prospéro-García, 2006).

Generally, it believed amongst the general public that consumption of CBD is associated with benefits to sleep and sleep quality- and CBD-based products are marketed as such. However, systematic review study by Whiting et al (2015) reviews CBD in the context of incidence of adverse events in randomized clinical trials which were inclusive of the use of cannabinoids (Whiting et al., 2015). The study includes a review of 79 trials (6462 participants) for sleep disorder and the following indications: nausea and vomiting due to chemotherapy, appetite stimulation in HIV/AIDS, chronic pain, spasticity due to multiple sclerosis or paraplegia, depression, anxiety disorder, psychosis, glaucoma, or Tourette syndrome. This systematic review concludes that there is moderate-quality evidence to support the use of cannabinoids for the treatment of chronic pain and spasticity. There was low-quality evidence suggesting that cannabinoids were associated with improvements in nausea and vomiting due to chemotherapy, weight gain in HIV infection, sleep disorders, and Tourette syndrome. Interestingly, cannabinoids were associated with an increased risk of short-term AEs (Whiting et al., 2015).

Sleep studies by Professor Mathew Walker, Professor of Neuroscience and Psychology at the University of California, Berkeley, USA- a world renowned expert in sleep and neuroscience- summaries the difference between the effects of THC & CBD on sleep onset and sleep quality. Prof THC will decrease the amount of time it takes you to fall asleep; but like alcohol and other sedatives, it blocks Rapid Eye Movement (REM) sleep. Whilst conversely, CBD seems to reduce the amount of time it takes one to fall asleep and acts to decrease anxiety which can improve sleep quality through thermoregulation. Interestingly, it is also sited that lower doses of CBD may also promote wakefulness. Again, suggesting that further investigation is required to unpick the mechanisms in which CBD and other cannabinoids effect latency and quality of sleep (Walker, 2019).

Central Nervous System Disorders and Diseases and CBD

The distribution and function of the components of the endocannabinoid system (ECS) in the central nervous system (CNS) and immune processes have garnished significant research focus with major milestones (Joshi & Onaivi, 2019). In this section we explore and table targets of CBD with potential therapeutic effects for CNS disorders and finalise with evidence of clinical research conducted on persons living with Parkinson's Disease (PD). Treatments for epilepsy are described earlier.

In summary of the literature as a whole CBD is very unlikely to exert effects in some identified cases of neurological diseases through modulation of the endocannabinoid system. The main reasons for this being that a number of other molecular targets of CBD reported in the literature are unlikely to be of relevance because the effects of 'treatment' are observed at supraphysiological concentrations. However, a study by Ibeas Bih et al aiming to surface molecular targets, showed that there are some plausible CBD targets following the exclusion of the most unlikely and implausible targets (Ibeas Bih et al., 2015). These neurological disease relevant therapeutic CBD targets the remaining molecular targets of CBD with plausible evidence for involvement in therapeutic effects in neurological disorders were associated with either the regulation of, or responses to changes in, intracellular calcium levels. At the time of this study, to the best of our knowledge there is no causal proof that CBD's effects at these targets, they represent the most probable for future investigations and further studies of CBD's therapeutic mechanism of action. In table below we insert estimated efficacious concentrations of CBD for each experimental scenario. This makes inroads in gauging applicable concentrations for future in-vivo and in-vitro research experiments. It is noteworthy that (i) several the concentrations identified in the studies found to have potential therapeutic effects are supraphysiological and (ii) our list consists of receptors as targets for CBD. There are also other targets such as enzyme targets, ion channel targets, and transporter channel targets which are outside the scope of this report and may be a consideration for future exploration. The systematic review paper by Ibeas Bih et al (2015) provides further detail on the associated of identified targets in epilepsy, movement disorders, neurodegenerative disorders (Alzheimer's disease and dementias) and inflammation-correlating mitochondrial dysfunction, oxidative stress and cell death mechanisms as an underlaying cause of neurodegenerative disorders and thus a suitable therapeutic target (Calì, Ottolini, & Brini, 2012; Currais, 2015; Hsieh & Yang, 2013).

Neurodegenerative disease

Parkinson's Disease

Parkinson's disease (PD) is a common and complex neurological disorder that encompasses a range of clinical, epidemiological, and genetic subtypes. PD can be categorised as the progressive loss of dopaminergic neurons in the substantia nigra leading to striatal dopamine depletion is the core mechanism underlying the cardinal motor features of PD. Although depletion of dopamine is the most notable neurotransmitter change in PD, other neurochemical changes occur and contribute to PD symptomatology. Many regions of the nervous system outside the basal ganglia are also involved in PD. The underlying molecular pathogenesis involves multiple pathways and mechanisms, such as α-synuclein proteostasis, mitochondrial function, oxidative stress, calcium homeostasis, axonal transport, and neuroinflammation (DeMaagd & Philip, 2015; Hirsch, Vyas, & Hunot, 2012; Park, Davis, & Sue, 2018; Rieder, 2020; Stoker, Torsney, & Barker, 2018).

PD is also associated with a number of both motor and non-motor symptoms that can be equally disabling. Pharmaceutical and medicinal approached that enhance intracerebral dopamine concentrations or stimulate dopamine receptors remain the main treatment for motor symptoms (Hirsch et al., 2012; Park et al., 2018). At time of writing, none of available treatments have proven to be neuroprotective or disease-modifying. Dopaminergic drugs are particularly effective during the early stages of the disease as they provide enhanced levels of neurotransmission. However, PD upon progression of the disease and long-term use, these medications often lead to reduced efficacy and the development of complications such as motor fluctuations and dyskinesias (Moustafa et al., 2016).

Unlike most of the motor features of PD, many non-motor symptoms do not respond to dopaminergic therapy, and some are indeed aggravated by them, with great impact on patient quality of life. The refractoriness of these symptoms to dopaminergic therapy implicates non-dopaminergic mechanisms. Therefore, current needs in the management of symptomatic patients with PD include dopamine-unresponsive axial motor impairments and non-motor symptoms, such as dementia, depression, anxiety, psychosis, and pain (DeMaagd & Philip, 2015). Due to the inherent complexity of PD, there is a clear need for therapeutic strategies which target combination of dopaminergic as well as non-dopaminergic systems in the brain.

Parkinson’s disease and CBD

As such there has been interest in cannabidiol (CBD) as a treatment option for PD because of the identification of multiple potential targets of action in the CNS. CBD is one of the many cannabinoids identified in Cannabis sativa, being the second most abundant constituent after Δ9-tetrahydrocannabinol (THC). Unlike THC, CBD is non-psychoactive, and has been ascribed many potential medical benefits.

A study from Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, Brazil, addressed animal and human clinical studies involving the use of CBD for PD. The group studied the effects of CBD in preclinical and clinical studies. This included open-label study [n=6 participants], a case series [n=4 participants], and a randomised control trial [n=26 participants].

The open-label study was entailed oral CBD administration of 150-400 mg/day. This was combined with general anti-parkinsons treatments and agents. The results indicated that there was a decrease in the psychotic symptoms evaluation [the Brief Psychiatric Rating Scale and the Parkinson Psychosis Questionnaire], with no evidence of impact on cognitive and motor symptoms. Moreover, there was no evidence of severe side effects (Zuardi et al., 2009).

The case series study included patients with Rapid Eye Movement (REM) behaviour disorder (RBD). Interestingly, there was evidence that all study participants experience a prolonged decrease in the frequency of RBD following CBD treatment. Furthermore, upon discontinuation of treatment the complex RBD movements returned to baseline frequency and intensity (Chagas et al., 2014).

In the third study, an exploratory double-blind trial of CBD versus placebo, participants without PD or psychiatric conditions were assigned to 3 groups and were treated with CBD 75 mg/day, or CBD 300 mg/day or placebo. The Unified Parkinson's Disease Rating Scale [UPDRS] was used to assess and score motor and general symptoms. Interestingly, the study showed that there was no difference across the 3 treatment groups. However, participants treated with CBD 300mg/day had a significantly different mean total score in the Parkinson’s Disease Questionnaire (PD-Q39)- a questionnaire which assesses how often people affected by Parkinson's experience difficulties across 8 dimensions of daily living. This was attributed to

the possible effect of CBD in improving measures related to quality of life in PD patients without psychiatric comorbidities (Chagas et al., 2014).

These studies showed interesting results, and indicate that there is potential for the use of CBD as a treatment for PD. However, sample sizes (participant numbers) are very low and the duration of follow-up was very short. The Movement Disorder Society Evidence- Based Medicine Committee recommendations for treatments of PD published in 2018 concluded that there was insufficient evidence to support the use of CBD for the treatment of PD at the time.

It is vital to note that no conclusions can be drawn on the efficacy of CBD in this setting, as larger phase III and conclusive efficacy trials have not been conducted in PD. Double-blind, placebo-controlled, randomized trials with larger samples of patients with PD are needed to elucidate the possible effectiveness and mechanisms involved in the therapeutic potential of CBD in PD. Additionally, studies conducted specifically to evaluate the safety profile of CBD in patients with PD (including long-term safety), possible interactions with antiparkinsonian drugs, and possible side effects, as well as the therapeutic window for motor and non-motor PD symptoms, are also required (Rieder, 2020).

Table 1: Receptor Targets of Cannabidiol

Target	Concentration range (μM)	EC_{50}/IC_{50} (μM)	K_i (μM)	Preparation or tissue	Assay type	Reference
CB_1	3; NSC	ND	ND	A549/human	Viability	(Ramer et al., 2013)
	3; NSC	ND	ND	H460/human	Viability	
	NSC	>10	ND	ND	ND	(Bisogno et al., 2001)
	NSC	>30	ND	HEK293 membrane/human	GTPγS	(Ryberg et al., 2007)
CB_2	3; NSC	ND	ND	A549/human	Viability	(Ramer et al., 2013)
	3; NSC	ND	ND	H460/human	Viability	
	NSC	>10	ND	ND	ND	(Bisogno et al., 2001)
	NSC	>30	ND	HEK293 membrane/human	GTPγS	(Ryberg et al., 2007)

Target	Concentration range (μM)	EC_{50}/IC_{50} (μM)	K_i (μM)	Preparation or tissue	Assay type	Reference
Glycine receptor α1 subunit	1–300; (+)	12.3	ND	HEK293/ND	Patch clamp/current with glycine	(Ahrens et al., 2009)
	1–300; (+)	132.4	ND	HEK293/ND	Patch clamp/current without glycine	
Glycine receptor α1β subunit	1–300; (+)	18.1	ND	HEK293/ND	Patch clamp/current with glycine	
	1–300; (+)	144.3	ND	HEK293/ND	Patch clamp/current without glycine	
Glycine receptor α3 subunit	0.01–50.00; (+)	3*	ND	HEK293/ND	Patch clamp/current without glycine	(Xiong et al., 2012)
GPR18	10^{-4}–100; (+)	51.1	ND	HEK293/ND	p44/42 MAPK activation	(McHugh, 2012)
GPR55	10^{-3}–1; (–)	0.45	ND	Human osteoclasts	Rho and ERK1/2 activation	(Whyte et al., 2009)

Target	Concentration range (μM)	EC_{50}/IC_{50} (μM)	K_i (μM)	Preparation or tissue	Assay type	Reference
	10^{-3}–10^{-2}; (–)	ND	ND	Colon	Contraction	(Li, Fichna, et al., 2013)
	(–)	0.445	ND	HEK293 membrane/human	GTPγS	(Ryberg et al., 2007)
5-HT_{1A}	8–32; (–)	ND	ND	CHO membrane/human	[3H]-8-OH-DPAT ligand binding	(Russo, Burnett, Hall, & Parker, 2005)
	16; (–)	ND	ND	CHO membrane/human	[35S]-GTPγS assay	
	16; (–)	ND	ND	CHO/human	Forskolin	
5-HT_{2A}	8–32; (+)	ND	ND	NIH 3T3 membrane/rat	[3H]-Ketanserin	
nAChR α-7	0.1–100.0; (–)	11.3	ND	*Xenopus* oocyte/human	Patch clamp/current/acetylcholine	(Mahgoub et al., 2013)
Opioid (δ)	0.1–100.0; (–)*	10.7*	18.4	Cerebral cortex membrane/rat	[3H]-NTI binding assay	(Kathmann, Flau, Redmer,

Target	Concentration range (µM)	EC_{50}/IC_{50} (µM)	K_i (µM)	Preparation or tissue	Assay type	Reference
Opioid (µ)	0.1–100.0; (-)*	10*	31.6	Cerebral cortex membrane/rat	[3H]-DAMGO binding assay	Tränkle, & Schlicker, 2006)
PPARγ	3; (+)	ND	ND	A549/human	mRNA RT-PCR/Western blot	(Ramer et al., 2013)
	3; (+)	ND	ND	H460/human	mRNA RT-PCR/Western blot	

Table 2. List of Potential Cellular/Receptor Targets. CB_1 = cannabinoid type 1; CB_2 = cannabinoid type 2; GPR = G protein-coupled receptor; 5-HT = serotonin; nAchR = nicotinic acetylcholine receptor; PPAR = peroxisome proliferator-activated receptor; NSC = no significant change; ND = not described; HEK = human embryonic kidney; CHO = Chinese hamster ovary; GTPγS = guanosine 5'-O-[gamma-thio]triphosphate; MAPK = mitogen-activated protein kinase; ERK = extracellular regulated kinase; [3H]-3-OH-DPAT = 7-(dipropylamino)-5,6,7,8-tetrahydronaphthalen-1-ol; [3H]-NTI = naltrindole; [3H]-DAMGO = D-Ala^2, N-$MePhe^4$, Gly-ol; RT-PCR = reverse transcription polymerase chain reaction; (+) = stimulation; (-) = inhibition Adapted from (Ibeas Bih et al., 2015).

**Estimated from plots in cited papers*

Anticancer Effects of CBD

Cancer is the second leading cause of death worldwide, and it accounts for about 8.8 million deaths in 2015 (GHO 2018 data); nearly 1 of 6 deaths is due to cancer. Cancer is a multistep disease characterized by a formation of a preneoplastic lesion (initiation processes) which, by time, progresses into malignant tumour. Generally, cell transformation is a combination of intrinsic genetic factors and external exposure to physical, chemical, and biological carcinogens. However, it must be underlined that ageing and lifestyle are others fundamental factors for the development of the disease. Indeed, the incidence of cancer rises dramatically with age, probably due to the decreased efficacy of cellular repair mechanisms, while tobacco, alcohol, unhealthy diet, and physical inactivity are the major global cancer risks.(Pellati et al., 2018)

In 1975, Munson et al demonstrative the anti-proliferative potential of CBD both in vitro and in vivo (Munson, Harris, Friedman, Dewey, & Carchman, 1975). Since then the number of studies published has only increased demonstrating the anticancer potential of CBD both in vivo and in vitro. These studies note that CBD can negatively impact tumour progression, cancer cell migration and adhesion while excreting pro-apoptotic, anti-invasive and anti-proliferative effects (Chakravarti, Ravi, & Ganju, 2014; Dariš, Tancer Verboten, Knez, & Ferk, 2019; I. Khan et al., 2016). The clinical use has also gradually grown year after year, with chemo-preventive effects of CBD in some types of cancers noted including lung, breast, prostate and colon (Munson et al., 1975; Rosengren & Cridge, 2013; Velasco, Hernández-Tiedra, Dávila, & Lorente, 2016).

Lung Cancer

Lung cancer is one of the most common causes of cancer deaths. In 2018, two million new cases of lung cancer had been reported worldwide (Azar et al., 2017).The main reported risk associated with lung cancer is smoking tabaco, reported to be associated with 90% of all cases.

In vitro, CBD treatment has been shown to inhibit cell invasion of the lung cancer cell line A549. This was liked with a decrease in the secretion of plasminogen activator inhbitior-1 (PAI-1) (Ramer, Rohde, Merkord, Rohde, & Hinz, 2010). In a separate study, it was reported that PAI-1 was key for the anti-metastatic potential of CBD. High level of PAI-1 is poor prognostic factor in many cancers (McMahon et al., 2001). CBD induced upregulation of ICAM-1 (Inter-intracellular adhesion molecule) has also been reported in vitro. Decreased expression by of ICAM-1 by lung cancers cells is mechanism which by the cancer cells evade the immune systems most notably lymphokine-activated killer (LAK) cells (Haustein, Ramer, Linnebacher, Manda, & Hinz, 2014).

Breast Cancer

Breast cancer is the primary cause of death among women. Risk of breast cancer is associated with several factors including family history, age and genetics (Kis et al., 2019). In vitro using the breast cancer cell lines MDA-MB-231 and MCF-7, CBD treatment has been shown to induce cell death associated with inhibition of AKT/mammalian target of rapamycin (mTOR) signalling and the enhanced production of reactive oxygen species (ROS) (Shrivastava, Kuzontkoski, Groopman, & Prasad, 2011). Furthermore, inhibition of epidermal growth factor induced proliferation and improved PPAR gamma nuclear localisation following CBD treatment in breast cancer cells has been noted (Elbaz et al., 2015; Sultan, Marie, & Sheweita, 2018).

Prostate Cancer

Prostate cancer is one of the most common cancers in men with 99% of cases occurring after the age of 50 (Rebbeck, 2017). CBD has been shown to be an inhibitor of cancer cell growth in the prostate cancer cell lines LNCaP and PC3 (Sharma, Hudson, Adomat, Guns, & Cox, 2014).CBD mediated inhibition of cell cell growth in PC3 cells in vitro, is linked with decreased exosome and microvesicle (EMV) biogenesis. EMV are lipid bilayer structures, released by cells that play a role in various pathologies including cancer, where increased EMV release is associated with chemo—resistance and transfer of pro-oncogenic factors (Kosgodage et al., 2018). In vitro treatment of LNCaP cells with CBD resulted in stimulation of the intrinsic pathways of apoptosis. The pro-apoptotic activity of CBD was noted to be phosphatase-dependent (Petrocellis et al., 2013).

Colon Cancer

Colon cancer is the second most common cancer in the world (DeSantis et al., 2014). CBD have been shown to have significant antiproliferative effects in Caco-2 and HCT116 colon cancer cell lines (Aviello et al., 2012). Using a mouse model of colon cancer treated with 1mg/kg of CBD significantly reduced both aberrant crypt foci (ACF) polyps and tumours in the mice. This protective effect of CBD on colon cancer has been associated with up-regulation of caspase-3 leading to apoptotic cell death (Aviello et al., 2012). Furthermore, a role for GPR55 has been implicated in the prevention of metastasis of colon cancer cells (Kargl et al., 2016).

Clinical evidence of anticancer effects of CBD

Information collected to date in relation to the anticancer effects of CBD are nearly completely limited to preclinical studies conducted on cell lines and animal models. Although there is a lot of literature on preclinical in vitro and in vivo studies that describe the anticancer mechanism of CBD on various types of cancer, the number of clinical trials which have as a research theme the study of the effect of CBD on different types of cancer is limited (Iffland & Grotenhermen, 2017). To discover the full scope of its positive effects on cancer, more human studies are needed to investigate the toxicological parameters. The risks about the long administration's effects are unknown, especially for children. Drug interaction studies are necessary from both a therapeutic and a safety viewpoint.

In terms of clinical trials, CBD was most studied for glioblastoma. In 2014, a clinical trial that analysed the effect of CBD as a single agent for solid tumour was conducted (clinical trial: NCT02255292). Another placebo-controlled phase II clinical trial analysed the effect of the combination of THC and CBD with adjuvant chemotherapy with temozolomide for patients with glioblastoma, and reported positive results using this approach (clinical trial: NCT01812603).

In 2018, a clinical trial with 119 cancer patients was conducted over a four-year framed period. Patients were given CBD oil three days on and three days off, with an average dose of 10 mg twice a day (max 30 mg for increased tumour mass). In this study, patients with different types of cancer (e.g., breast, prostate, and oesophageal) were included. From 119 cancer patients, the most stunning case was a 5-year-old male patient with anaplastic ependymoma, a very rare brain tumour. He started the treatment with CBD oil in February 2016, and in December 2016 the relevant scans showed that tumour volume had decreased by approximately 60%. The other patients from this study have reported that the side effects completely disappeared, and although the duration of treatment was six months, many continued the treatment (Kenyon, Liu, & Dalgleish, 2018).

Another case study presents an 81-year-old woman who was diagnosed with ovarian cancer in March 2017. The patient declined all interventions due to the treatment toxicity. She started with alternative therapy CBD oil (1 drop sublingually/day) and Laetrile tablets, which contain purified amygdalin (500 mg 4 times/day). After two months, CT imaging showed a dramatic decrease in the size of the tumour (Barrie, Gushue, & Eskander, 2019).

Immunomodulatory Effects of CBD

The immune systems encompass various cell types acting together to provide protection against foreign invaders while simultaneously avoiding reactions against self-proteins. The innate immune system which reacts quickly to destroy pathogens comprises of myeloid cells including neutrophils, monocytes, and macrophages. When the innate immune response is insufficient, cells of the innate immune system activates the adaptive immune response which is comprised predominantly of T cells and B cells. Activation of T cells provides signals that enable requitement and activation of other immune cells such as the case of stimulating B cells to produce antibodies to neutralise the pathogen or enhance destruction of the pathogen. T cells can also directly act of the infected cells resulting in lyse or apoptosis.

The effects of CBD on the immune system can directly affect both the innate or adaptive responses for example by modulating cytokine production by the cells the immune systems or by enhancing the production of reactive oxygen species or peroxidases by these cells.

Effect of CBD on the innate immune system

One of earliest effects reported with CBD was in human mononuclear cells (Watzl, Scuderi, & Watson, 1991b, 1991a), in which TNF-α, IFN-γ, and IL-1α were all suppressed (0.01–20 μg/mL CBD or 0.03–64 μM CBD). Later studies focused on human monocytic cells revealed that CBD can induce apoptosis in either HL-60 (1–8 μg/mL CBD or 3.2–26 μM CBD) (Gallily et al., 2003) or primary human monocytic cells (1–16 μM CBD)(Wu et al., 2010; Wu, Huang, Lin, Wang, & Jan, 2018). Macrophages are also targets, although they have been studied more commonly in animal models. Peritoneal macrophages were used early on to demonstrate that CBD (3 μg/mL or 10 μM) targets nitric oxide (Coffey, Yamamoto, Snella, & Pross, 1996), and this has also been a well-studied target of suppression by CBD in many tissues and cell types. The mechanism by which CBD suppressed nitric oxide involves suppression of endothelial (Costa, Giagnoni, Franke, Trovato, & Colleoni, 2004)or inducible nitric oxide synthase (iNOS) (Esposito et al., 2007) in response to various inflammatory stimuli. iNOS is known to be regulated by the transcription factor nuclear factor-κB (NF-κB) (Kleinert, Pautz, Linker, & Schwarz, 2004) , which is comprised of p65 and other proteins, and becomes active after degradation of the inhibitory protein, IκB. Decreased expression of iNOS by CBD correlated with stimulation of the inhibitory IκBα protein and inhibition of NF-κB p65 protein expression (Mukhopadhyay et al., 2011). Using peritoneal macrophages from diabetic mice stimulated *ex vivo* with LPS revealed that macrophages isolated from CBD-treated mice did not produce as much TNF-α or IL-6 as macrophages isolated from vehicle-treated mice (L. Weiss et al., 2006). A direct effect of CBD decreasing macrophage numbers in the bronchoalveolar lavage fluid was shown following intranasal LPS administration to induce pulmonary inflammation (Alison Ribeiro et al., 2012). There was also decreased expression of F4/80 (a marker of macrophages) mRNA expression by CBD in heart tissue in experimental autoimmune myocarditis (Lee et al., 2016). Although this study identified CBD only affecting F4/80 mRNA expression as opposed to F4/80 cell surface staining, it does suggest a novel target (i.e., heart tissue) of CBD in a relatively understudied autoimmune model.

IL-6 is a proinflammatory cytokine produced by many cell types, predominantly innate cells. Many studies have shown that circulating IL-6 is readily inhibited by CBD in inflammatory models, including diabetes (Lola Weiss et al., 2008), asthma (Vuolo et al., 2015), pancreatitis (Nichols & Kaplan, 2020), and hepatitis (Hegde, Nagarkatti, & Nagarkatti, 2011). CBD treatment *in vivo* resulted in lower IL-6 production in peritoneal macrophages stimulated *ex vivo* with LPS (Li, Feng, et al., 2013; Lola Weiss et al., 2008), in the pancreas in acute pancreatitis (Li, Feng, et al., 2013), and in bronchoalveolar lavage fluid in LPS-induced pulmonary inflammation (Hayakawa et al., 2007) .

There have been some reports that CBD alters neutrophil function. Compromised MPO activity by CBD has been studied in several tissues, including brain, colon (Jamontt, Molleman, Pertwee, & Parsons, 2010)(Alison Ribeiro et al., 2012), lung (A. Ribeiro et al., 2015), and pancreas (Li, Feng, et al., 2013). In the pulmonary inflammation studies with LPS, neutrophil cell counts in the bronchoalveolar lavage fluid were also decreased by CBD compared to LPS (A. Ribeiro et al., 2015). Together, the results suggest that CBD's mechanism for neutrophil suppression involves both decreased numbers of neutrophils and compromised MPO activity.

Effect of CBD on the adaptive immune system

Investigations into the effects of CBD on the adaptive immune response have primarily focuses on T cells. Inhibition of interferon gamma (INF-g) production by phytohemagglutinin (PHA) stimulated T cells in the presence of 0.01-20 ug/ml or 0.03-64 uM has been reported (Watzl et al., 1991b). Further studies have shown that IGNg production from lymph notes cells isolated from arthritic mice and INF-g production from splenocytes stimulated ex vivo can be inhibited in the presence of CBD treatment (Malfait et al., 2000; L. Weiss et al., 2006) and In studies using mouse splenocytes a 30-min pre-treatment with CBD (0.1–20 μM) suppressed IFN-γ in response to PMA/Io or anti-CD3/CD28 (Kaplan, Springs, & Kaminski, 2008).It was further shown that the mechanism by which CBD suppressed IFN-γ occurred at the level of transcription and that two important transcription factors for IFN-γ, activator protein-1 (AP-1) and nuclear factor of activated T cells (NFAT), were inhibited by CBD, suggesting a transcriptional mechanism for suppression (Kaplan et al., 2008). Given the reports that IFN-γ seems to be a target of suppression by CBD, it was surprising that *Ifng* mRNA was not affected by CBD (5 μM) using encephalitogenic T cells stimulated by antigen-presenting cells (APCs) and myelin oligodendrocyte glycoprotein peptide ($MOG_{35–55}$) *in vitro* (Kozela et al., 2016). However, CBD did inhibit expression of IFN-γ receptor 1 and CBD increased several IFN-γ-responsive genes known to attenuate T cell proliferation (Kozela et al., 2016). The data reveal that an important part of CBD's action in the immune system is its ability to affect IFN-γ in multiple ways. Not only did CBD directly suppress IFN-γ production through a transcriptional mechanism but also suppressed IFN-γ receptor expression.

Other T cell-derived cytokines have been demonstrated as targets of CBD. IL-6 production is suppressed by CBD (5 μM) using encephalitogenic T cells stimulated by APCs and $MOG_{35–55}$*in vitro*, and “IL-6 signalling” as a critical pathway is suppressed by CBD (Kozela et al., 2016, 2013). Furthermore “IL-17 signalling” was also identified as a critical pathway suppressed by CBD (5 μM) in T cells *in vitro.* IL-6 promotes the differentiation of TH17 cells(Zhou et al., 2007; Zimmerman, Zimmerman, Cameron, & Laurence, 1977), so the simultaneous suppression of IL-6 and IL-17A by CBD is consistent with CBD suppressing TH17 cell differentiation. CBD (1–20 μg/mL or 3.2–64 μM) suppressed IL-17A production in human $CD3^+$ T cells (derived from healthy patients or patients with MS or non-seminomatous germ cell tumours) stimulated *ex vivo* with PMA/Io (Zgair et al., 2017).

There few studies in which B cells are identified as targets of CBD. CBD given at 25 mg/kg by intraperitoneal (i.p.) injection reduced the sRBC-induced plaque-forming cells, a measure of antibody production. A similar study using oral administration of CBD found inhibition of antibody production (Kaplan et al., 2008). Other studies have shown that CBD robustly inhibited the sRBC-induced antibody production *in vitro* (Kaplan et al., 2008), suppressed ovalbumin-induced IgM, IgG1, and IgG2a in an *in vivo* asthma model (Jan, Su, Wu, & Liao, 2007), and reduced expression of activation markers such as major histocompatibility complex II, CD25, and CD69, on B cells (Kozela et al., 2015). CBD has also been shown to induce apoptosis in B cells (Wu et al., 2008). Overall, the results suggest that B cells can be targets of suppression by CBD.

Immune enhancement by CBD

Much of the data support the fact that CBD is immune suppressive and anti-inflammatory; however, there are reports of CBD resulting in immune enhancing effects. This has been attributed to differences in hormetic (i.e., biphasic) responses depending on CBD concentration/dose, cell culture conditions, including serum presence and/or percent, immune stimulant, and magnitude of cellular activation in response to the immune stimulant. Some have shown that CBD can either enhance or suppress cytokine production (IL-2 and IFN-γ) in response to relatively low or high degree of immune stimulation (Chen et al., 2012). The mechanism for the differential responsiveness likely involves alterations in intracellular calcium, as CBD increases intracellular calcium in mouse splenocytes regardless of the increase of intracellular calcium produced by the immune stimulant. In addition, the differential cytokine production was correlated with nuclear expression of the NFAT transcription factor, which is calcium responsive. Interestingly, CBD's ability to increase intracellular calcium also likely accounts for some of the other enhancing effects, including stimulation of neutrophil degranulation (Naccache, Volpi, Becker, Makryannis, & Sha'afi, 1982), chemotaxis (Walter et al., 2003), and mast cell/basophil activation (Giudice et al., 2007).

In the final section of the literature review we will identify and consolidate further examples of CBD application identified in research journal papers. The section will consolidate a brief summary of evidence supporting the potential use of CBD and CBD-containing products in veterinarian practice.

Furthermore, working alongside the Accelerate team, the HH now have greater levels of experience undertaking collaborative R&D projects with academia and a further understanding of innovation processes more generally. Potential areas for future consideration in relation to the products ongoing development might include further exploring the evaluation of products with end-users in general, health and social care, further enhancing marketing strategy and capabilities and continuity of engagement with academia, health& wellbeing, fitness, health care and social care stakeholders. This project lays the foundations for potential future collaborative studies. This preliminary study concludes as "The European Union's highest court ruled that cannabidiol (CBD) isn't a narcotic drug.
The decision by the Court of Justice of the European Union (CJEU) is a setback for EU countries that are cracking down on CBD products, arguing they are harmful to people's health" https://www.politico.eu/article/cjeu-rules-that-cbd-is-not-a-narcotic-drug/ (Accessed 19.04.2021)

Veterinary Applications and CBD for Pets

'The global CBD pet market size was valued at USD 27.7 million in 2019 and is expected to grow at a compound annual growth rate (CAGR) of 40.3% from 2020 to 2027. The perceived benefits of cannabis, high awareness among pet owners, and preference for natural pet supplements have led to an upsurge in market growth. The benefits of CBD based products in fixing physical and mental issues in pets are driving the market. According to the Cannabis product news report, around 24.0% of the U.S. pet owners consume CBD based products either for themselves or for their pets. Pet CBD treatment has been found useful in treating diseases like cancer, anxiety, sleep disorders, and epilepsy. Rising incidences of anxiety disorder in pets especially dogs is another growth propelling factor for the market' (GVR, 2019) .

To conclude the literature review we bring our focus to case studies of CBD benefits in Animals. There is evidence in the literature which supports the use of CBD in Veterinarian practise. Thus, representing an opportunity for CBD & CBD-derived products in this sector. For example, the *VetCompassTM programme* collects clinical data on dogs attending UK primary-care veterinary practices. The study included all VetCompassTM dogs under veterinary care during 2013. Candidate osteoarthritis cases were identified using multiple search strategies. A random subset was manually evaluated against a case definition. Of 455,557 study dogs, 16,437 candidate osteoarthritis cases were identified; 6104 (37%) were manually checked and 4196 (69% of sample) were confirmed as cases. Estimated annual period prevalence (accounting for subsampling) of appendicular osteoarthritis was 2.5% (CI95: 2.4–2.5%) equating to around 200,000 UK affected dogs annually. Risk factors associated with osteoarthritis diagnosis included breed (e.g. Labrador, Golden Retriever), being insured, being neutered, of higher bodyweight and being older than eight years. Duration calculation trials suggest osteoarthritis affects 11.4% of affected individuals' lifespan, providing further evidence for substantial impact of osteoarthritis on canine welfare at the individual and population level (Anderson et al., 2018).

There is supporting evidence in the literature for use of CBD as an anti-arthritic treatment. In this section will consolidate a summary of evidence supporting the potential use of CBD and CBD-containing products in veterinarian practice. The articles in the table below highlight evidence for use of CBD the veterinarian practice as anti-osteoarthritic, anti-inflammatory, anti-epileptic and pain management agents to promote health and wellbeing of animals.

Table 2. Case Studies of CBD Benefits in Animals

Case Study	Objectives	Methodology	Results	Clinical Significance	Reference
Article 1: Pharmacokinetics, Safety, and Clinical Efficacy of Cannabidiol Treatment in Osteoarthritic Dogs	The objectives of this study were to determine basic oral pharmacokinetics and assess safety and analgesic efficacy of a cannabidiol (CBD) based oil in dogs with osteoarthritis (OA).	Single-dose pharmacokinetics was performed using two different doses of CBD enriched (2 and 8 mg/kg) oil. Thereafter, a randomized placebo-controlled, veterinarian, and owner blinded, cross-over study was conducted. Dogs received two treatments: CBD oil (2 mg/kg) or placebo oil every 12 h. Each treatment lasted for 4 weeks with a 2-week washout period. Baseline veterinary assessment and owner questionnaires were completed before initiating each treatment and at weeks 2 and 4. Hematology, serum chemistry and physical examinations were performed at each visit. A mixed model analysis, analyzing the change from enrollment baseline for all other time points was utilized for all variables of interest, with a $p \leq 0.05$ defined as significant. ***CBD Oil and Protocol:*** 10 mg/mL of CBD as an equal mix of CBD and carboxylic acid of CBD (CBDa), 0.24 mg/mL tetrahydrocannabinol (THC), 0.27 mg/mL cannabichromene (CBC), and 0.11 mg/mL cannabigerol (CBG); all other cannabinoids were less than 0.01 mg/mL.	Pharmacokinetics revealed an elimination half-life of 4.2 h at both doses and no observable side effects. Clinically, canine brief pain inventory and Hudson activity scores showed a significant decrease in pain and increase in activity ($p < 0.01$) with CBD oil. Veterinary assessment showed decreased pain during CBD treatment ($p < 0.02$). No side effects were reported by owners; however, serum chemistry showed an increase in alkaline phosphatase during CBD treatment ($p < 0.01$).	This pharmacokinetic and clinical study suggests that 2 mg/kg of CBD twice daily can help increase comfort and activity in dogs with OA.	(Gamble et al., 2018)
Article 2: Randomized Blinded Controlled Clinical Trial to Assess the Effect of Oral Cannabidiol Administration in Addition to Conventional Antiepileptic Treatment on Seizure Frequency in Dogs With Intractable Idiopathic Epilepsy	To assess the effect of oral cannabidiol (CBD) administration in addition to conventional antiepileptic treatment on seizure frequency in dogs with idiopathic epilepsy.	This study involved 26 client-owned dogs with intractable idiopathic epilepsy. Dogs were randomly assigned to a CBD (n = 12) or placebo (14) group. The CBD group received CBD-infused oil (2.5 mg/kg [1.1 mg/lb], PO) twice daily for 12 weeks in addition to existing antiepileptic treatments, and the placebo group received noninfused oil under the same conditions. Seizure activity, adverse effects, and plasma CBD concentrations were compared between groups. ***CBD Oil and Protocol:*** CBD-infused oil (2.5 mg/kg [1.1 mg/lb], PO) twice daily for 12 weeks in addition to existing antiepileptic treatments	CBD group had a significant (median, 33%) reduction in seizure frequency, compared with the placebo group. Proportion of dogs considered responders to treatment (≥ 50% decrease in seizure activity) was similar between groups. N=2 CBD group developed ataxia and were withdrawn from the study. N=9 in the CBD group & N=7 in the placebo group were included in the analysis. Plasma CBD concentrations correlated with reduction in seizure frequency. Dogs in the CBD group had significant increase in serum alkaline phosphatase activity.	Significant reduction in seizure frequency was achieved in the CBD group, the proportion of responders was similar between groups. Given the correlation between plasma CBD concentration and seizure frequency, additional research is warranted to determine whether a higher dosage of CBD would be effective in reducing seizure activity by ≥ 50%. No adverse behavioural effects were reported by owners.	(McGrath, Bartner, Rao, Packer, & Gustafson, 2019)

Article 3: Preliminary Investigation of the Safety of Escalating Cannabinoid Doses in Healthy Dogs	To determine the safety and tolerability of escalating doses of three cannabis oil formulations, containing predominantly CBD, THC, or CBD and THC (1.5:1) vs. placebo in dogs.	Randomized, placebo-controlled, blinded, parallel study involving twenty(n=20) healthy Beagle dogs (n=10 males, n=10 females). Dogs were randomly assigned to one of five treatment groups (n = 4 dogs per group balanced by sex): CBD-predominant oil, THC-predominant oil, CBD/THC-predominant oil (1.5:1), sunflower oil placebo, medium-chain triglyceride oil placebo. Up to 10 escalating doses of the oils were planned for administration via oral gavage, with at least 3 days separating doses. Clinical observations, physical examinations, complete blood counts, clinical chemistry, and plasma cannabinoids were used to assess safety, tolerability, and the occurrence of adverse events (AEs). AEs were rated as mild, moderate, or severe/medically significant. ***CBD oil and protocol:*** CBD-predominant oil, THC-predominant oil, CBD/THC-predominant oil (1.5 :1), sunflower oil placebo, medium-chain triglyceride oil placebo. - CBD oil up to the tenth dose (640.5 mg; ~62 mg/kg), - THC oil up to the tenth dose (597.6 mg; ~49 mg/kg) - CBD/THC oil up to the fifth dose (140.8/96.6 mg CBD/THC; ~12 mg/kg CBD + 8 mg/kg THC).	Dose escalation of the CBD-predominant oil formulation was shown to be as safe as placebo and safer than dose escalation of oils containing THC (CBD/THC oil or THC oil). The placebo oils were delivered up to 10 escalating volumes, the CBD oil up to the tenth dose (640.5 mg; ~62 mg/kg), the THC oil up to the tenth dose (597.6 mg; ~49 mg/kg), and the CBD/THC oil up to the fifth dose (140.8/96.6 mg CBD/THC; ~12 mg/kg CBD + 8 mg/kg THC). AEs were reported in all dogs across the five groups and the majority (94.9%) were mild. Moderate AEs (4.4% of all AEs) and severe/medically significant AEs (0.8% of all AEs) manifested as constitutional (lethargy, hypothermia) or neurological (ataxia) symptoms and mainly occurred across the two groups receiving oils containing THC (CBD/THC oil or THC oil).	Overall, dogs tolerated dose escalation of the CBD oil well, experiencing only mild AEs. The favorable safety profile of 10 escalating doses of a CBD oil containing 18.3–640.5 mg CBD per dose (~2–62 mg/kg) provides comparative evidence that, at our investigated doses, a CBD-predominant oil formulation was safer and more tolerated in dogs than oil formulations containing higher concentrations of THC.	(Vaughn, Kulpa, & Paulionis, 2020)
Article 4: Transdermal cannabidiol reduces inflammation and pain-related behaviours in a rat model of arthritis – 2016	Current arthritis treatments often have side-effects attributable to active compounds as well as route of administration. Cannabidiol (CBD) attenuates inflammation and pain without side-effects, but CBD is hydrophobic and has poor oral bioavailability. Topical drug application avoids gastrointestinal administration, first pass	This study examined efficacy of transdermal CBD for reduction in inflammation and pain, assessing any adverse effects in a rat complete Freund's adjuvant-induced monoarthritic knee joint model. CBD gels (0.6, 3.1, 6.2 or 62.3 mg/day) were applied for 4 consecutive days after arthritis induction. Joint circumference and immune cell invasion in histological sections were measured to indicate level of inflammation. Paw withdrawal latency (PWL) in response to noxious heat stimulation determined nociceptive sensitization, and exploratory behaviour ascertained animal's activity level.	Measurement of plasma CBD concentration provided by transdermal absorption revealed linearity with 0.6–6.2 mg/day doses. Transdermal CBD gel significantly reduced joint swelling, limb posture scores as a rating of spontaneous pain, immune cell infiltration and thickening of the synovial membrane in a dose-dependent manner. PWL recovered to near baseline	These data indicate that topical CBD application has therapeutic potential for relief of arthritis pain-related behaviours and inflammation without evident side-effects.	(Hammell et al., 2016)

	metabolism, providing more constant plasma levels.	CBD and protocol: CBD gels (0.6, 3.1, 6.2 or 62.3 mg/day) were applied for 4 consecutive days after arthritis induction	level. Immunohistochemical analysis of spinal cord (CGRP, OX42) and dorsal root ganglia (TNFα) revealed dose-dependent reductions of pro-inflammatory biomarkers. Results showed 6.2 and 62 mg/day were effective doses. Exploratory behaviour was not altered by CBD indicating limited effect on higher brain function.		
Article 5: Cannabinoid-mediated Antinociception Is Enhanced in Rat Osteoarthritic Knees	To determine whether local administration of the cannabinoid 1 (CB (1)) receptor agonist arachidonyl-2-chloroethylamide (ACEA) can modulate joint nociception in control rat knee joints and in experimental osteoarthritis (OA).	OA was induced in male Wistar rats by intraarticular injection of 3 mg of sodium mono-iodoacetate, with a recovery period of 14 days. Electrophysiologic recordings were made of knee joint primary afferent nerve fibres in response to normal rotation and noxious hyper-rotation of the joint both before and after close intraarterial injection of different doses of ACEA.	Local application of the CB(1) agonist significantly reduced the firing rate of afferent nerve fibres by up to 50% in control knee joints (n=19) and up to 62% in OA knee joints (n=29; P<0.01). Coadministration of the CB (1) receptor antagonist AM251 or the transient receptor potential vanilloid 1 (TRPV-1) ion channel antagonist SB366791 significantly reduced the desensitizing effect of ACEA. The CB (1) receptor antagonist AM251 by itself had no effect in the control joint but significantly increased the firing rate of afferent nerve fibers in the OA joint.	These findings indicate that activation of peripheral CB (1) receptors reduces the mechanosensitivity of afferent nerve fibers in control and OA knee joints. Blockade of either the CB (1) receptor or the TRPV-1 channel significantly reduced the efficacy of ACEA, which suggests that both receptors are involved in cannabinoid-mediated antinociception. The increased nerve activity observed following CB(1) receptor antagonism suggests a tonic release of endocannabinoids during OA. As such, peripheral CB(1) receptors may be important targets in controlling OA pain	(Schuelert & McDougall, 2008)

Report Summary

The Report explores CBD and the potential for application of CBD-based products in health, well-being, and disease treatments. We learn about the historical context and use of CBD in traditional medicine practises before exploring growth of hemp plant and the landscape of CBD-derived pharmaceuticals currently supplied in the market. *See Introduction and Cannabis Seed to Plant.*

We show approved CBD-based pharmaceuticals ("Medical Cannabis") Epidiolex®, Nabilone (Cesamet®) and Nabiximols (Sativex) currently approved for alleviation of symptoms associated will multiple complex diseases in children and adults suffering rare, severe forms of epilepsy; adults suffering with side effects of chemotherapy such as nausea and vomiting, and for Multiple Sclerosis (MS) patients suffering with muscle stiffness and spasms. *See CBD & Cannabis-based products in the market and as pharmaceutical(s).*

Following this we literature on stress, anxiety and sleep and role effects of CBD in these areas of quality of life; and the CBD in Prevention and Treatment of Central Nervous System Disorders and Diseases- specifically neurodegenerative diseases such as Alzheimer's Disease and Parkinson's Disease. Here we have also highlighted targets of CBD previously identified in in-vitro and in-vivo studies for their association with potential for diseases therapy for neurodegenerative disease and breast, bowel, prostate, colon and lung cancers. *See 'stress, anxiety and sleep' & 'CBD in Prevention and Treatment of Central Nervous System Disorders and Diseases'*

We provide list of literature-derived cellular receptor targets for CBD and explore the downstream physiobiological pathways effected by CBD and CBD derived compounds through investigation of in-vitro and in-vivo research studies and clinical studies. Through this we see a multiplicity of opportunities for further in-vitro, in-vivo, pre-clinical and clinical medical research in areas of neuroscience, oncology, immunity and beyond. *See 'anti-cancer effects of CBD' and 'Neurodegenerative disease: Parkinson's disease'.*

However, it is clear that further research is required to in this area not least to unpick the underlaying mechanisms which underpin the beneficial, and in cases adverse, effect of CBD; but also in generating a deeper understanding and knowledge of its pharmacokinetic profile with larger human cohort studies (Chagas et al., 2014).

Furthermore, we look at comprehensive evidence of modulatory effects on the innate and adaptive immunity and opportunities in this area to support disease prevention and treatment. *See Immunomodulatory Effects of CBD.*

To conclude the literature review, we provide evidence supporting the promotion of health and wellbeing in pets and potential for veterinarian use as an anti-inflammatory, anti-osteoarthritic, anti-inflammatory, anti-epileptic and pain management agent. This represents a large market potential CBD pet product such as those manufactured by Hemp Heros. In 2019 the Pet CBD market was valued at 27.7 million USD ; and is on a trajectory to meet a CAGR of 40.3% between 2020 and 2027 (GVR, 2019). *See Veterinary Applications- CBD for Pets.*

In the next section we make recommendations for next steps and future collaborative research initiatives.

Outline Recommendations for Future Work

By undertaking the task of reviewing existing literature, it is clear that research databases have a comprehensive quantity of related research articles and as a result the most relevant and topic related research articles were selected for closer inspection to understand the current thinking around the medical and non-medical uses of CBD-based products in the market. This body of literature was used to identify areas in which Hemp Heros and HTC Accelerate/Swansea University could collaborate further. In light of this we have identified areas for potential future collaboration between Hemp Heros and SU/HTC Accelerate.

In-vitro laboratory studies in disease areas -use of Accelerate Facilities to conduct feasibility studies which will enhance offering to research grant applications.

- Testing of products from Hemp Heros on a variety of fundamental disease models starting with in-vitro studies. These studies may include those with the use of immortalised cells to mimic wound healing, cancer, neurodegenerative disease, obesity and others to provide a wide range and fundamental understanding of further avenues for CBD-based disease interventions. Taking specific interest in potential cellular targets and pathway modulation effects.
- Research include assays focusing on inflammation, mitochondrial dysfunction, oxidative stress and cell death mechanisms underpinning neurodegenerative diseases such as Alzheimer's and Parkinson's disease and others.

Sleep and recovery studies in humans. This would include tests which explore the use of Hemp Heros products in the context of sleep and recovery. In order to facilitate this HTC Accelerate will make introductions to the managers at Swansea University Sleep Lab to initiate discussions. We will also look to engage with relevant and interested academics across SU faculties, schools and colleges. Engagement in this activity will likely require human and capital resources beyond the scope of HTC Accelerate Programme and therefore research grant applications should be sought to satisfy the requirements.

Marketing Analysis- develop an understanding of what CBD/CBDA product end user look for in products to inform RD&I activity, product development and marketing. HTC Accelerate should link the team with the outreach and engagement team at Swansea University School of Management. In addition there is opportunities to form student projects aligned to industry challenges. Steer should also be given to HTC Accelerates partner programme, AGOR-IP. AGOR-IP are well placed to seek additional support for Hemp Heros on market analysis, product life-cycles, IP-generation, IP-capture, commercialisation/exploitation of existing on future products. HTC Accelerate can also offer support to this agenda. For example: the co-develop a quick questionnaire with School of Management colleagues to collect the perspectives of students or the general public on Hemp Heros products to inform marketing strategy or future product development; or collect data on wellbeing benefits of CBD-based product use and consolidate findings from verified product users.

Additional Suggestion for Collaborative Research.

We conclude the report by suggesting areas of future research to leverage pre-requisite knowledge, skills and capabilities at Hemp Heros and Swansea University and engage in exciting and rigorous collaborative initiatives to provide next steps in collaborative activities to benefit Hemp Heros and the University. The collaborative team would be advised to pursue research grant applications to further these initial RD&I activities. Some additional recommendations are outlined below:

We propose that future ***SU-Hemp Heros research initiatives seek external research grant funding and*** the inclusion of a multi-disciplinary team approach. **A list of lab tests and experiments and** areas for research are below:

As a result of our preliminary literature review. We have identified laboratory test which would deliver a greater understanding of the potential beneficial and therapeutic effects of CBD in various disease contexts. The potential areas for future investigation have been synthesised based on skills, expertise and specialised laboratory equipment at HTC Accelerate and their affiliate network. Additional Future studies could include:

- **Antiparasitic** – To investigate the antiparasitic activity, *upon* exposure to various concentrations of the product (CBD). Isolation of CBD or derivative compounds would be required for such a study.

- **Anti-inflammatory** – Impact of both the innate and adaptive immune system should be considered. To investigate the impact of the product of the inflammatory response of the innate immune system, initial investigations should in stimulation of the innate cells with a stereotypical inflammatory inducer e.g. LPS +/- the extract with cytokine production, cell death and cell activation status considered as outputs. A similar approach can be devised for the adaptive response, however the inflammatory stimulus in this case would differ e.g. PHA/Cytostim (Zhen et al., 2015). Further work can then be carried out to determine the mode of action. Once basic mechanisms are understood, this route of investigation could be expanded to the anti-inflammatory activity in disease specific contexts e.g. IBD

- **Anti-aging** – Two avenues of investigation could be taken under the umbrella of anti-aging. One avenue is to examine ageing of the skin as defined by the cosmetic industry. To ability of to the product as an anti-elastase, anti-collagenase and anti-hyaluronidase in addition to its ability to inhibit free radical product in skin cells could be considered (Ndlovu, Fouche, Tselanyane, Cordier, & Steenkamp, 2013). The second would be the impact on cellular senescence. To investigate this, both normal and senescent cells would be subject to various concentrations of the product with total cell counts, MTT viability screening, senescence-associated beta-galactosidase activity and p53 (a marker of cellular senescence) phosphorylation as potential outputs (Hooten & Evans, 2017; Yang, 2010).

- **Antifungal** – To determine antifungal activity yeast growth (e.g. Candida albicans) can be analysed over time while subjected to various concentration of the product. The test realises a viable cell count, checking whether a drug has fungistatic or fungicidal action. Micromorphological evaluations of the yeast could also be investigated noting differences in fungal growth structure in the presence of the product (Leite, Bezerra, Sousa, Guerra, & Lima, 2014). Further work can then be carried out to determine the mode of action.

- **Antimicrobial/Antibacterial** – The antibacterial potency should be evaluated using both gram positive (e.g. Staphylococcus aureus and Bacillus cereus) and gram negative (Escherichia coli, Salmonella typhi and Pseudomonas aeruginosa) bacteria. Antimicrobial activity can be evaluated using the disk diffusion method. Following this the minimum inhibitory concentration (MIC) can be determined (Mostafa et al., 2018). Further work can then be carried out to determine the mode of action.

Research Funding Applications

To effectively deliver on follow-up on larger proposed avenues for future research we should consider research grant applications to buy out human resource and capital. The provided are examples only. Other relevant calls are available and cycle throughout the calendar year.

UKRI/Innovate UK- Case for CBD vs CBD-A effects in human and non-human disease models- effectiveness – receptor identification/characterisation on immune and tissue specific cells (neurons, immune cells); testing versus disease paradigms/assays. Prof Cathy Thornton and Dr Jeff Davies. PHD/Masters Project**-** Knowledge Transfer Partnership. Co-development of Knowledge Transfer Partnership between SU and HempHeros would further embed the company in the universities ecosystem and provide dedicated resource to conduct RD&I activities to solve challenges with university support. At time of writing the Welsh Government are subsidising total project costs for SMEs from 33% to 25%. The application window for the subsided support is will continue until June 2021; and will return to 33% thereafter.

British Academy of Management- SAMS/BAM Research and Capacity Building grants are aimed at researchers who want to develop an empirical research project that: Enables capacity building by bringing together a group of researchers from at least two HE institutions, including early career as well as experienced researchers. Produces novel conceptual outcomes based on rigorous, innovative use of methods and by developing original ways of thinking to address complex management problems. Demonstrates the social value of management research conducted in the public interest. This type of grant could be applied for to leverage skills and expertise across Medical and Management school. An example here might be to consolidate best practise and cultivation methodologies for optimisation during development of local manufacturing facilities, as well as supply and value chain research.

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