

CBD AS A FUTURE FOOD

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CBD has gained huge market attention and interest from a wide range of industries and consumers; as food ingredient, beverage extract, food supplement and medicinal compound.

OVERVIEW

Cannabis is believed to be one of the oldest domestic crops dating back 6000 years. The taller and more sturdy crops were bred with other crops showing similar characteristics, leading to the strain of cannabis known as hemp which was used to make a variety of foods, oils and textiles, rope and fabrics. Cannabidiol (CBD) is a naturally occurring cannabinoid higher in the hemp strains which has gained great attention for its associated benefits to human health and wellbeing. The shorter, bushier plants were identified as having psychoactive properties and were selectively bred for recreational, medicinal and religious purposes, leading to the unique strains of cannabis commonly known as Marijuana and illegal in the UK, with the exception of recent medical approval for prescription under strict provisions (NICE Guidelines, 2020).

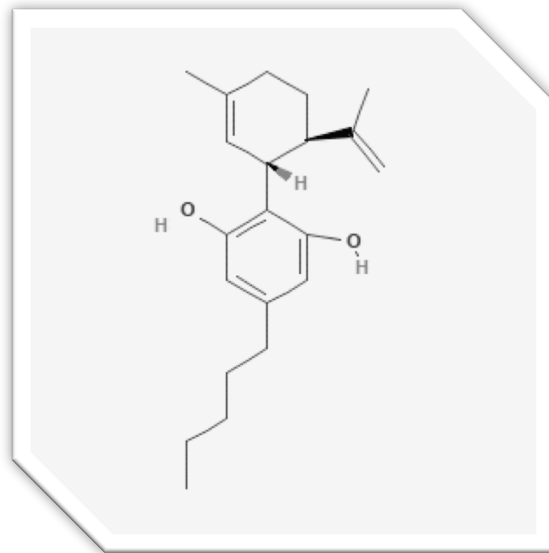


Figure 1; Structure of Cannabidiol (CBD) the compound found naturally in hemp and associated with benefits to human health

CBD is a, 21-terpenophenolic compound, formed from decarboxylation of the cannabidiolic acid precursor in the plant but can also be produced synthetically. CBD extracted oil has demonstrated effectiveness as a treatment in several clinical trials for some neurological and physiological conditions. CBD use in humans is deemed as being free from the risk of dependence or abuse. However, ill effects can be expected in counterfeit, unregulated or substandard products (WHO, 2019).

MARKET

The CBD market is driven by the \$49bn herbal supplement market, the growing anxiety economy and the rise in the legal cannabinoid marketplace. CBD compounds can be used by multiple industries; human health, pet health, pharmaceutical, nutraceutical and food and beverage ingredients, claiming a wide array of health attributes. Due to such rapid growth the market worth for CBD is not comprehensive nor robust, however, in 2015 the CBD market worth was \$2.6bn, with growth projected to exceed \$26.6bn by 2025; a CAGR of 34% (MarketWatch, 2019). There are still large gaps in the research knowledge and health associations of CBD and due to its growth, the regulation has been inconsistent, but this has not prevented consumer interest or held back consumers from purchasing or losing interest. The versatility and associated benefits of CBD see it as a product which is going to make waves for many years to come (Forbes, 2019). Whilst CBD has attracted global interest, the largest market is

seen in Europe where there has been the most growth, consumer demand and interest (Euromonitor International, 2020).

LAW

The legal situation is complicated, with countries having their own laws. In the USA, for example, there are differing laws from state to state. In the UK the laws around CBD are more uniform where cannabidiol products are legal when derived from EU approved strains of hemp.

Table 1; Legal strains of hemp for agricultural use, approved by the EU (Home Office- Drugs Licensing & Compliance, 2020).

#	VARIETY NAME	COMMON CATALOGUE STATUS
1	ADZELVIEŠI	REGISTERED
2	ARMANCA	REGISTERED
3	ASSO	REGISTERED
4	AUSTA SK	REGISTERED
5	BALATON	REGISTERED
6	BENIKO	REGISTERED
7	BIALOBRZESKIE	REGISTERED
8	BIAŁOBRZESKIE	REGISTERED
9	CS	DELETED; WITH MARKET EXTENSION UNTIL 30.06.2021
10	CANNAKOMP	REGISTERED

CBD, in its pure form, is not classed as a controlled substance in the UK, but due to CBD being derived from a plant species that is illegal to grow, the need for clear boundaries is paramount. Cannabis itself is currently a controlled drug under the Misuse of Drugs Act, 1971. As the law is complex, there are common misinterpretations of the law surrounding CBD and this misinformation is a major concern as it can be misleading.

Any product containing CBD that is used for medicinal purposes is classed as a medicine and must have a product license, CBD products must therefore avoid making any medical claim or act as a medicinal product or it will face enforcement by the Medicines and Healthcare products Regulatory Agency (MHRA). However, certain CBD products are subject to domestic law in respect of rules governing food, or cosmetics, where legal status is determined by a separate set of factors dependent on the intended market.

The Home Office issues licences for the cultivation of cannabis plants with a low tetrahydrocannabinol (THC) content (<0.2%) to produce hemp fibre, seeds and oil. A granted licence enables the use of the non-controlled seeds, stalk and fibre of the plant. In order to obtain a licence, the Home Office requires full details of the intended commercial use. Furthermore, the licence will only be issued for approved seed varieties to ensure the THC level is not exceeded. The 0.2% maximum content of THC is enforced to differentiate between legal and illegal strains, where detected levels of THC >0.2% come under The Misuse of Drugs Regulations, 2010 (The Misuse of Drugs, 2010).

The regulations around hemp have been regarded by some in the industry as no longer fit for purpose and the legal framework that impacts CBD products is considered out of date, as the applicable regulations for CBD were enacted in 2001, prior to the emergence of the growing consumer market in cannabidiol containing products.

The most important new legal development arises from the European Union's Novel Food regime, which led to the classification of all extracted cannabinoids as novel, in January 2019. As currently drafted, it presents a serious challenge to the CBD market as it exists in the UK today - however it is yet to be enforced in the UK.

NOVEL FOODS; EU STAND ON CBD

EU member states now categorise food, drink and food supplements containing CBD as 'novel foods'. A key part of novel food regulation is premarket authorisation, which means that any manufacturer intending to put CBD into food is required to apply to the European Commission via an online application. EFSA states that a novel food is classed as;

'a food that had not been consumed to a significant degree by humans in the EU before 15th May 1997'
(EFSA, 2020).

In January 2019, the European Commission updated the Novel Food listings to state that extracts of *Cannabis sativa* L., and derived products containing cannabinoids, are considered as novel foods, as a history of consumption has not been demonstrated within European populations. As a result, all extracts of hemp and derived products containing cannabinoids (including CBD) are now regarded by the European Commission as 'novel'. This categorisation applies to the extracts themselves, and any products to which they are added as an ingredient (such as hemp seed oil). Synthetically obtained cannabinoids are also considered to be novel.

The Novel Food Catalogue is not legally binding but is used as a reference by many authorities in the EU for the purposes of the Novel Food Regulation ((EU) 2015/2283). This change to the Novel Food Catalogue may, therefore, mean that authorities in the member states refuse to permit supply of foods and food supplements containing cannabinoids, awaiting formal approval by the European Food Standards Agency (EFSA) under the Novel Food Regulation.

This will be tested by the outcome of the first application to the EFSA for a CBD food, which was submitted by Cannabis Pharma SRO, for a food supplement containing CBD for adults with a daily intake of up to 130mg. EFSA announced at the beginning of June 2019, that the European Commission are currently examining the application request, which if granted, will then be subjected to further technical and scientific assessment. If the application is successful, the European Commission will issue an implementing regulation adding CBD as a food/ingredient to the list of approved novel foods. Approval will also specify any applicable conditions of use such as maximal doses, daily intakes, age limitations and labelling requirements. Any product which differs from the approval will require an additional application under the Novel Food Regulation (EFSA, 2018).

In the meantime, manufacturers, distributors and consumers in the EU market may find that the sales of CBD containing products is disrupted by the transitional provisions of the Novel Foods Regulation, but they will still be sold and not removed providing that the regulation is adhered to.

Example of novel foods where CBD is used;

- CBD oils, capsules and oral spray
- CBD gummies, mints and other sweets
- CBD infused tea, coffee, beer and soft drinks
- CBD snacks including energy bars

All cannabis strains contain cannabinoids, with up to 60 different cannabinoids discovered to date. THC is the compound associated with the psychoactive properties and getting 'high'. Psychoactive cannabis strains contain up to 30% THC, whereas, hemp strains contain very little (<0.2%). (de la Fuente et al., 2019). Psychoactive cannabis is

illegal in the UK and many other countries, but the hemp strain of cannabis is legal, together with extracted CBD oil in supplements, infusions, extracts, ingredients and essential oils.

The following cannabinoids are prohibited;

- Natural cannabinoids, e.g. cannabis, hashish and marijuana
- Synthetic cannabinoids e.g. D9-tetrahydrocannabinol (THC) and other cannabimimetic compounds

Hemp is also much higher in CBD than other strains of cannabis. CBD is the most abundant cannabinoid, naturally present within industrial hemp plants and its extracts. It is non-psychoactive, non-intoxicating and not known to be addictive. Furthermore, CBD is considered to be well tolerated in humans (Bitencourt and Takahashi 2018). Extracting CBD from hemp is done by cold pressing, ethanol extraction or CO₂ extraction. Once extracted the CBD can be left raw and added to consumer products without further need for processing, or it can be distilled to remove elements such as chlorophyll.

As the industry continues to grow EFSA anticipate that additional classifications will be enforced in CBD food and beverage products.

Additionally, The World Health Organisation (WHO) released a statement that CBD poses 'no health problems' and is not harmful' (Manthey, 2019), and the World Anti-Doping Agency (WADA) stated that 'Cannabidiol is no longer prohibited' (WADA 2019).

FOOD MANUFACTURING

The use of CBD infused products has attracted NPD in both small- and large-scale businesses. The challenges arise in food manufacture due to the chemical make-up of CBD. The chemical makeup of CBD makes it a stable compound when chilled and stored at a stable temperature, but studies show degradation if temperatures rise and that the product has a relatively short shelf life in its pure form.

CBD is hydrophobic and therefore not water soluble, but is lipophilic, binding to, and soluble, in lipids. These factors are of interest in the method of delivery used within foods and beverages/liquids. Here the advances of nanoencapsulation in beverages can be utilised to ensure compound uptake and the use of oils to imbue the CBD. The use of nanoencapsulation also allows the use of CBD in consumables without any undesired change to taste, but the addition needs consideration to the effect on olfactory, texture and ingredient composition of the product. Current and developmental methods of delivery are required to be thoroughly considered when adding CBD to foods, as well as the storage of the CBD and the end infused product.

It must be noted that CBD infused products cannot be sold in the US and are prohibited by the Food and Drug Administration (FDA) (FDA, 2020).

REGULATIONS FOR CBD IN THE UK

- Importing CBD: No strict requirements apply for importing CBD into the UK, provided that the THC content is found to be 0.2% or lower by Border Control.
- Selling CBD: A licence is not required to sell CBD in the UK provided THC is not detected or <0.2% and this is verified by an ISO accredited laboratory.
- CBD flowers: The sale of 'CBD flowers' and buds are prohibited even if THC is below the permitted THC 0.2% content and from EU approved origin.
- CBD food: Adding CBD to food/food supplement requires a novel food application but the authorities appear not to be enforcing this requirement to date.

- Applying for a license: Applying for novel food status or any other type of license relating to CBD, or hemp, requires significant resources. For hemp to be grown for the CBD extraction, growers must apply for and hold a Hemp Growing Licence (HGL) from HMRC.
- It is considered that the enforcement by the UK authorities has been slack and, therefore, is the reason why prohibited products, such as CBD flowers and unlicensed CBD foods, without novel food designation can be purchased in UK shops.
- Selling CBD in other EU markets: Each EU member state has their own laws on CBD and seeking expert advice is advised to navigate local laws within the EU.

Whilst the official updated CBD regulations are currently being written and reviewed, some trade associations, including the Cannabis Trade Association (CTA), has used existing regulation as a guide to make their own proposed rules. The CTA offers an insight into what some in the industry believe should be included in the new CBD regulations but whether their proposal influences the new regulations in the UK and EU is uncertain.

PACKAGING REGULATIONS

Labelling must not mislead the consumer, hold medical claims, health or nutritional claims and must clearly display the percentage of CBD contained. The labelling must also clearly state the manufacturer's address and the full ingredient list (Arrowsmith, 2019).

WHY WOULD CBD BE BENEFICIAL TO HUMAN HEALTH?

The endocannabinoid system within the human body is a naturally occurring system that regulates a variety of physiological processes associated with mood, memory and motor function. When cannabinoids are consumed, they bind with the endocannabinoid receptors in the brain and immune system. The effects on the human body differ depending on the receptors activated and the concentration of cannabinoid consumed. Restrictions surrounding the use of some cannabinoids has limited research into the body's interaction and the effects. However, in rodents' high levels of cannabinoids have shown to negatively affect reproduction by acting at different sites, particularly THC (Walker, Holloway and Raha, 2019).

Endocannabinoids have been demonstrated to be important modulators in the response of the hypothalamus, pituitary and adrenals stress response axis, during repetitive-stress conditions and in pathological conditions, such as anxiety, phobias, depression, and posttraumatic stress disorders (Hill and Tasker, 2012).

Over the past few years, it has become evident that multiple mechanisms, not solely limited to the central nervous system, are involved in the endocannabinoid-mediated control of food intake and energy balance (Gamage and Lichtman, 2011). This potential clinical use may help clarify how the endocannabinoid system affects physiological functions and the pathology of diseases related to hormonal secretion and energy balance.

Following a review of the currently available data, NICE published guidelines in November 2019 ([NICE Guideline NG144](#)) for the use of cannabis based medicinal products (CBMPs) to treat a range of conditions for which they had been suggested as effective.

These were

- Intractable chemotherapy induced nausea and vomiting
- Severe treatment resistant epilepsy
- Spasticity
- Chronic pain

NICE's role is to review the available evidence and make recommendations based on the cost-benefit analysis of treatments. One of the problems they encountered when reviewing the evidence on the effectiveness of cannabidiols was that much of the data was anecdotal and not based on strong statistical evidence, and they recommended that more research was needed to show efficacy.

- 27 studies on intractable chemotherapy induced nausea and vomiting were identified which examined the clinical effectiveness of cannabis-based medicinal products (CBMPs) and it was recommended that nabilone, a synthetic cannabinoid which mimics THC, could be used to treat adults if conventional antiemetics had not been effective.
- [Epidyolex](#) is the only CBMP available for epilepsy and is licensed specifically for use in Dravet and Lennox-Gastaut syndromes. Individual patients who have seizures, which are not controlled by other medicines, have reported a reduced number of seizures when taking the epidyolex. However, the data is limited, and the committee concluded that it was difficult to assess how effective and safe CBMPs are for the treatment of people with epilepsy, and could not issue a general guideline. They did, however, recommend not removing CBMP treatment from those severely affected individuals who were seeing significant improvement in the frequency of their seizures.
- [Sativex](#) is a THC:CBD spray which is licensed in the UK for treating spasticity in people suffering from multiple sclerosis. The evidence reviewed showed that there were reductions in some measures of patient-reported spasticity using the Sativex spray and no increased incidence of adverse effects over those seen in the placebo groups, although much of the evidence was not of high quality. The committee agreed that the spray could be recommended to treat moderate to severe spasticity in adults with multiple sclerosis if other pharmacological treatments had not been effective, but noted that no other CBMPs had been sufficiently tested.
- The evidence reviewed showed that there was a limited pain reducing effect when cannabis was used and there was no reduction in the use of opioid based pain killers when medicinal cannabis was prescribed as an add on. More research is needed on patients with fibromyalgia, intractable cancer related pain and pain associated with childhood diseases to see if cannabis products could be used to reduce the levels of opioid based pain killers used and allow more patients to be treated in an outpatient setting.

ATTRIBUTED BENEFITS OF CBD

CBD's antioxidant and anti-inflammatory properties have been widely acknowledged and subjected to multiple studies; yet more research is required to accredit CBDs therapeutic effects. Many CBD based products are available to buy within stores and online, but levels of the desired compounds have significantly varied in 'off the shelf' lab analysis (Gallily 2018).

Table 2; List of the main identified cannabinoids and their associated health attributes.

COMPOUND	PROPERTIES
CANNABIDIVARIN (CBDV)	Like THCV, CHDV differs from CBD only by the substitution of a pentyl (5 carbon) for a propyl (3 carbon) sidechain. Although research on CHDV is still in its infancy, emerging studies have demonstrated promise for its use in epilepsy management. This is due to its action on TRPV1 receptors and modulation of gene expression.
CANNABIGEROL (CBG)	A non-psychoactive cannabinoid, CBG'S antibacterial effects can alter the overall effects of cannabis. CBG is thought to kill or slow bacterial growth, reduce inflammation, (particularly in its acidic CBGA form,) inhibit cell growth in tumour/cancer cells, and promote bone growth. It acts as a low-affinity antagonist at the CB1 receptor. CBG pharmacological activity at the CB2 receptor is currently unknown.
CANNABICHROMENE (CBC)	CBC is most frequently found in tropical cannabis varieties. CBC is known to relieve pain, reduce inflammation, inhibit cell growth in tumour/cancer cells, and promote bone growth. The effects of CBS appear to be mediated through non-cannabinoid receptor interactions.
CANNABINOL (CBN)	CBN is a mildly psychoactive cannabinoid that is produced from the degradation of THC. There is usually very little to no CBN in a fresh plant. CBN acts as a weak agonist at both the CB1 and CB2 receptors, with greater affinity for CB2 receptors than CB1. The degradation of THC into CBN is often described as creating a sedative effect.
TETRAHYDROCANNABINOLIC ACID (THCA)	THCA is the main constituent in raw cannabis. THCA converts to Δ9-THC when burned, vaporized, or heated at a certain temperature. THCA, CBDA, CBGA, and other acidic cannabinoids hold the most COX-1 AND COX-2 inhibition, contributing to cannabis' anti-inflammatory effects. This cannabinoid also acts as an antiproliferative and antispasmodic.
TETRAHYDROCANNABINOL (THC)	The most abundant cannabinoid within marijuana, THC is responsible for cannabis' most well-known psychoactive effects. THC acts as a partial agonist at the CB1 AND CB2 receptors. The compound is a mild analgesic, or painkiller, and cellular research has shown that it has antioxidant activity.
TETRAHYDROCANNABIVARIN (THCV)	THCV is a minor cannabinoid found in only some strains of cannabis. The only structural difference between THCV and THC is the presence of a propyl (3 carbon) group, rather than a pentyl (5 carbon) group, on the molecule. Though this variation may seem subtle, it causes THCV to produce very different effects than THC. These effects include a reduction in panic attacks, suppression of appetite, and the promotion of bone growth. THCV acts as an antagonist at the CB1 receptor and a partial agonist at the CB2 receptor.
CANNABIDIOL (CBD)	CBD has been regarded as having tremendous medical potential. This is particularly true when the correct ratio of CBD to THC is applied to treat a condition. CBD acts as an antagonist at both the CB1 and cb2 receptors, yet it has a low binding affinity for both. This suggests that CBD's mechanism of action is mediated by other receptors in the brain and body.
CANNABIDIOLIC ACID (CBDA)	CBDA, similar to THCA, is the main constituent in cannabis with elevated CBD levels. CBDA selectively inhibits the COX-2 enzyme, contributing to cannabis' anti-inflammatory effects.

Cannabinoid list compiled and adapted from Correa et al., 2005 and National Hemp Association, 2018.

CONSUMER NEED-TO-KNOW

- Purchasing CBD can be confusing when multiple applications and delivery sources are available; CBD water, sweets, oils, gels and food additives. The stability of the CBD is dependent on current storage and what the CBD is added to/bound to. Unless nanoencapsulation is used an oil-based solute is most effective in its delivery.
- The packaging of the CBD product is paramount for the stability and delivery of the CBD to initiate any of the associated effects. As the oils degrades when exposed to light, it is essential that the bottles used are brown, green or black, and not clear, as has been the case in products such as 'CBD water'.
- It also must be stated that CBD does not have any approved EFSA health claims and suggestion that CBD has accredited health/nutritional claims must not be implied. Proposed benefits cannot be featured on packaging, labelling, advertising or marketing. This can be confusing when CBD has gained a lot of media attention with many anecdotally giving credit to CBD for improved health and medical status and due to cannabis oil now being available on prescription for certain medical purposes.
- Clear labelling of the CBD content should be present on the package and compliant to regulations, as stated above.

- CO₂ extraction is reported to be the most effective extraction method to ensure the properties of CBD are maintained and to prevent rancidity or degradation. Therefore, the consumer should select a product containing CBD from this extraction process.
- Safe THC content is essential to ensure the product is legal and does not possess any psychoactive effects. All THC content should be <0.2%.
- The CBD purchased should be free from toxins- only laboratory test results can confirm this.

Credible retailers will hold certificates of the CBD content, ingredients, heavy metal content, method of extraction, and organic certification and this should be on display or available on request for the consumer to view and verify the product's laboratory test results and authenticity.

FUTURE

Some EU countries have been left unsure of the laws and confused by the regulatory changes of CBD to a novel food and as a result have responded by placing restrictions on the sale of CBD and CBD containing products. At the same time, consumers have been left confused as to which CBD products have authorisation for sale by EFSA and the EU regulatory bodies, and which are safe.

Once the scientific research is provided and collated by EFSA an application for authorisation is expected to be submitted, so that CBD can then be marketed and sold with more clarity. For now, the novel foods regulations are the standard to adhere to.

The collation of clinical research is highly anticipated and is predicted to gain insight to the potential health benefits associated with the CBD compound.

Conclusion

CBD presents exciting opportunities for the food and beverage industry, as CBD-infused products increasingly become part of the market driven by consumer demand. CBD has made a great impact in a relatively small amount of time within the food, beverage, medical and nutraceutical industries, sparking innovation, research and development to facilitate the appropriate usage and application of CBD. However, the CBD marketplace can be confusing, for consumers and manufacturers; especially for those sourcing CBD. This is not likely to be made clearer until EFSA release a scientific review, which was anticipated in January 2020, but is yet to be made public.

Existing regulation has made the CBD space more controlled but has a way to go. The need for reliable and secure supply chains will improve the industries manufacturing process by making it more transparent and gaining much-needed trust within CBD products. A secure and regulated CBD oil supply chain will be the key to ensuring that the products contains what it claims.

Ever since CBD products started to hit the UK (and global) market following regulatory changes a few years ago, the media has been full of conflicting stories regarding its safety and efficacy. Questions continue to emerge and will probably continue to do so for a long time surrounding its usage and effects; is CBD a dangerous way of supplying cannabis to the mainstream market, or is it an effective alternative medicine?

What is clear is that CBD is here to stay.

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