Cannabidiol: a medicine, health supplement or foodstuff? Analysis of South African policies relating to the introduction of cannabidiol into the market.

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Declaration

I declare that this thesis that I now submit for assessment on the programme of study leading to the degree Master of Science in Pharmacy Administration and Policy Regulation has not been submitted for the purpose of a degree at this or any other higher education institution. It is entirely my own work and has not been taken from the work of others save to the extent that such work has been cited and acknowledged within the text of this work.

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''I can do all things through Christ who gives me strength.'' – Philippians 4:13

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Abstract

With the recent rise in the popularity of cannabidiol (CBD) around the world, there are many cultivators, manufacturers, and sellers of CBD on the market. It is sold in different dosage forms including oils, used to treat a wide variety of lifestyle diseases and medical conditions. Despite the increasing availability of CBD and its products, there are many controversies and uncertainties regarding the legality and regulation thereof in various countries. The main question is whether CBD is regarded as a medicine, health supplement or merely a foodstuff. This has led to CBD being placed under careful examination by numerous groups including agricultural activists, national health authorities, the World Health Organization (WHO), and the Food and Drug Administration (FDA). In South Africa (SA), CBD is also widely available as products that claims to enhance general health and even as supplements in foods and beverages. The aim of this study was to determine if CBD is classified as a medicine, health supplement or foodstuff in SA and whether South African policies and appropriate legislation is in place to effectively regulate the CBD market. To explore this research question, a qualitative explorative research approach was followed, and a scoping review was conducted where literature was reviewed to explore how medicines, health supplements and foodstuffs are registered in SA and to identify any shortcomings in the relevant policies and legislation. Policies and laws governing other countries including Australia, the European Union (EU) and the United States (US) were also reviewed to understand how CBD is regulated elsewhere and to use as a benchmark against which SA policies can be viewed. The study concluded that in SA, CBD can be classified as a medicine, health supplement or food depending on the concentration of the CBD present in the product. This is similar to what was found in Australia, whereas in the US, CBD is not allowed in dietary supplements and in the EU, it is either a medicine or classified as a novel food. SA has a National Cannabis Master Plan in development, with policies and legislation currently being implemented.

Keywords: Cannabis, cannabidiol, policies, regulation, legal status, medicines, health supplements, foodstuff, South Africa, European Union, United States, Australia

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List of Abbreviations

ARTG	Australian Register of Therapeutic Goods
ACT	Australian Capital Territory
AD	Anno Domini
BC	Before Christ
CB	Cannabinoid
CBD	Cannabidiol
CMC	Chemistry, manufacturing and control
CND	Commission on Narcotic Drugs
CoA	Certificate of Analysis
CTD	Common Technical Document
EFSA	European Food Safety authority
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FSANZ	Food Standards Australia New Zealand
GRAS	Generally recognized as safe
HACCP	Hazard analysis and critical control point
ICH	International Council for Harmonisation
OTC	Over the counter
SA	South Africa
SAHPRA	South African Health Products Regulatory Authority
TGA	Therapeutic Goods Administration
THC	Tetrahydrocannabinol
UK	United Kingdom
UN	United Nations
US	United States
WHO	World Health Organization

Chapter 1

Introduction, aims and objectives

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1. Introduction

1.1 Background

The cannabis plant has a long history of medicinal and recreational use. Cannabis is among the earliest plants cultivated by man, where evidence of its cultivation for fibers were found in China dating back to 4000 B.C. (Li & Lin, 1974). The ancient Chinese used cannabis seeds orally for medicinal purposes including constipation, rheumatic pain and others which are reported in the *pen-ts'ao ching*, the world's oldest pharmacopoeia compiled during the first century of this Era (Touwn, 1981). The Chinese used the cannabis fruits as food, but with the introduction of new cultures during the beginning of the Christian Era, it was no longer an important food in China, although the seeds are still used in Nepal to make kitchen oil (Touwn, 1981). In India, cannabis has been cultivated since 900 B.C. and used for its medicinal properties in *Ayurvedic medicine* (Kuddus *et al*, 2013).

In Africa, cannabis has been used since at least the 15th century, with its introduction probably through Arab traders that had connections to India (Du Toit, 1980). Cannabis arrived in SA during the 1650's with the European settlers and the crops were used in various ways. In the African society, the dried flowers of the cannabis plant were mainly smoked for its associated psycho-active effects and pain relief (Duvall, 2019). During the late 19th and early 20th centuries, control over cannabis was developed through national and international initiatives, with SA among the first countries to prohibit the use of cannabis in 1870 (Bewley-Taylor *et al*, 2014). A prohibitionist framework was established by the United Nation's Commission on Narcotic Drugs (CND) to control cannabis through the Single Convention on Narcotic Drugs of 1961 (Bewley-Taylor *et al*, 2014).

In recent years, the aspects of cannabis for medicinal use have been debated globally (ElSohly & Slade, 2005). With the isolation and discovery of 70 distinctive phytocannabinoids, with the two main phytocannabinoids namely cannabidiol (CBD) and tetrahydrocannabinol (THC), insight into the pharmacological effects and therapeutic benefits of cannabis was provided (ElSohly & Slade, 2005; Pertwee, 2006). There are several studies suggesting that CBD can be used to effectively treat epilepsy and other disorders including schizophrenia and anxiety, also exerting anti-inflammatory properties (Rong *et al.,* 2017). Due to the variety of pharmacological actions exhibited by CBD, the social, cultural, and legal viewpoints regarding the use of CBD based products have changed drastically, becoming more acceptable socially and culturally and being more readily available and accessible to the public in recent years (Mead, 2017). Currently Epidiolex® (containing 100 mg/ml CBD) oral solution is the only pure CBD product registered with the Food and Drug Administration (FDA) in the United States (US) and European Medicines Agency (EMA) indicated for a severe form of epilepsy in children (SAHPRA, 2020a). Despite all this research evidence, it was only at the end of 2020 that the CND voted to de-schedule cannabis from Schedule I to Schedule IV of the 1961 Single Convention on Narcotic Drugs,

where it was previously recognised as having no therapeutic or medicinal use (UN, 2020).

1.2 Motivation for the study (including problem statement or research question)

Forbes magazine, as well as other publications listed the top 10 food trends for 2019, with cannabis in foodstuffs as one of them (FACTS, 2019). These health and food trends have also led to an increase in the use of CBD in the South African market, where CBD containing products can be found in the pharmaceutical, as well as the food and beverage industry. Hazenkamp (2018) noted that CBD products may still be easily available in countries where CBD use is technically illegal, because authorities are laidback to enforce laws and, in many cases, discussions are continuing, on how to deal with the influx of CBD containing products.

In SA, the regulation of cannabis and CBD is also in progress. In 2018, the Constitutional Court of SA ruled that the right to privacy entitles adults to cultivate, possess or use cannabis for private use (Lubaale & Mavundla, 2019). This has led to confusion from the public as to the legal status of cannabis use. Even though the private use of cannabis has been decriminalised, manufacturing and selling of cannabis and CBD products is still regulated by the South African Health Products Regulatory Authority (SAHPRA). The South African government led by the Department of Agriculture, Land Reform and Rural Development (DALRRD) has developed a National Cannabis Master Plan for SA, which presents an integrated approach towards unlocking the economic potential of hemp and dagga (marijuana) by providing a framework for the establishment, development, and growth of the cannabis industry (DALRRD, 2021). Version 5 of the master plan is to be subjected to consultation with key stakeholders, that include government, labour, business and communities and the process of co-creation with relevant social partners is currently underway (DALRRD, 2021).

With the increase of CBD products into the SA market, as either medicines and health supplements, or food supplements, it creates uncertainty of current regulations regarding CBD, and it begs the question whether policies and regulations implemented in SA are ready to effectively regulate this market. With this in mind, the following research question is raised: How could the supply and sale of CBD and related products be regulated or controlled in the South African market?

1.3 Overall aims and objectives

The overall aim of this study was to determine the classification and subsequent registration of CBD containing products in SA and whether the South African regulatory system was ready to effectively regulate or control the introduction of CBD in the market.

The objectives of the study were to:

- Explore what CBD products are used for.
- Explore the current South African policies and regulations for medicines, health supplements and foodstuffs in relation to CBD products.

- Determine how these policies and regulations affect the introduction of CBD into the South African market by comparing them to other selected markets including the EU, US, and Australia.

1.4 Conclusion

Chapter 1 serves as a brief introduction to the study and concludes the necessity to investigate the CBD market and its subsequent regulatory environment in SA.

Chapter 2

Literature review

2.1 Introduction

In the literature review, the cannabis plant will be explored including the history of traditional uses and methods of administration, constituents of cannabis as well as cannabidiol (CBD). The legal status of CBD in SA, Australia, the EU, and US will be reviewed, also considering registration of medicines, health supplements and foods in these respective countries.

2.2 Uses of cannabis

The cannabis plant is regarded as one of the most versatile crops, cultivated as a source of food, fibre and medicine (Oultram *et al*., 2021). It has vast economic, social, and industrial value and can be used to produce textiles, clothing, paper, biofuel, biodegradable plastics, paint, animal feed and food (Cerino *et al*, 2021).

The first use of cannabis was found in China where the plant was used for fibres, with evidence dating back to 4000 B.C. These fibres were used to make strings, ropes, textiles, and paper (Li & Lin, 1974). The fruits of cannabis plant were also used by the Chinese as food, but during the beginning of the Christian Era it became a less important food (Touwn, 1981). Cannabis was used by the ancient Chinese as a medicine, with oral traditions being passed down from 2700 B.C. and later compiled into the oldest pharmacopoeia (*pen-ts'ao ching*) in the first century of this Era (Touwn, 1981). The founder of Chinese surgery, Hua T'o (110 – 207 A.D.) used a part of the cannabis plant with wine to anesthetise patients for surgery (Li & Lin, 1974). The seeds of the cannabis plant were mainly used by the Chinese as a medicine, and these seeds are still used today as a laxative by physicians in China (Touwn, 1981). The first evidence of cannabis being a psychoactive drug is mentioned in the *pen-ts'ao ching* with the word ''ma-fen'' meaning the fruits of cannabis and a phrase translating to excess intake of the fruits will produce visions of devils and over a long period of time allow you to communicate with spirits and lightens the body (Li, 1978).

Cannabis use in India for medicinal and recreational purposes was widespread, as the plant was assigned sacred virtues, thus associating it with religion. Cannabis is noted as one of the five sacred plants, mentioned in the *Atharva Veda*, a collection of sacred texts (Touwn, 1981). The plant was cultivated as early as 900 B.C. and its medicinal uses discovered in *Ayurvedic medicine* (Kuddus *et al*, 2013). The plant was used for many medicinal purposes such as analgesic, hypnotic, sedative, anaesthetic, antibiotic, anti-inflammatory, diuretic, expectorant, to name a few (Aldrich, 1997; Mikuriya, 1969). Due to the way it was prepared, the plant's psychoactive effects were well known in India. There were at least three preparations including *Bhang*, the weakest type made from dry leaves with the flowers carefully removed, *Ganja*, a stronger type prepared from the female plant's flowers and *Charas*, the strongest made exclusively from the resin that covers the female flowers (Touwn, 1981).

The use of cannabis in Africa has been recorded since at least the 15th century and was probably introduced by Arab traders with connections to India. This is suggested by the similarity in terms used in India and Africa for the preparation of the plant. Uses for the plant in Africa included fever, malaria, asthma, blood poisoning, dysentery, and snake bites amongst others (Du Toit, 1980). Cannabis was used in several ways in African culture, but it was most notably used as a smoked drug, where the flowers were dried before it was smoked (Duvall, 2019). In SA, the use of cannabis or dagga as it is known locally has a long history. Rural growers have cultivated dagga for many years, where it was harvested and sold in the bigger cities and towns mainly for recreational use (DALRRD, 2021). In addition to being called dagga, cannabis is also known as grass, weed, pot, dope, reefer, and ganja (FBTCC, 2021).

2.3 The cannabis plant

The cannabis plant belongs to the flowering family *Cannabaceae*, with the genus *Cannabis* and sub species. Domestication of the cannabis plant for human use has led to conflicting evolutionary interpretation and classification of cannabis. Small (2015) recommends that cannabis must only be classified as *Cannabis sativa* L. while other sources categorise the four species as *C. sativa*, *C. indica*, *C. ruderalis* and *C. afghanica* (Clarke & Merlin, 2013). A representation of male and female plants is shown in figure 2.1 below.

Figure 2.1: Painting of *Cannabis sativa* from Köhler (1887). **A** Flowering male

branch. **B** Fruiting female branch. **C** Cluster of male flowers. **D** Fruit (achene) surrounded by perigonal bract. **E** View of wide (flat) side of achene. **F** View of narrow side of achene. **G** Pistil, showing ovary and two stigmatic branches. **H** Pistil surrounded by young perigonal bract.

The cannabis plant contains many cannabinoids that exhibit activity on the cannabinoid receptors and can be categorized into three groups namely endocannabinoids (endogenous), phytocannabinoids (plant based) and synthetic cannabinoids (Fraguas-Sánchez *et al*., 2016). With the discovery of phytocannabinoids, research into cannabis has increased significantly, as it is a unique source of at least 66 phytocannabinoids (Pertwee, 2006). Phytocannabinoids and other compounds are secreted by granular trichomes, situated in the resin glands of the flowers of the female cannabis plants (Clarke & Watson, 2002). Cannabinoids are compounds that can be isolated, with CBD and Tetrahydrocannabinol (THC) as the two main compounds found in medicinal cannabis products. These compounds have different pharmacological properties, but CBD does not have any psychoactive effects as THC does (Leung, 2011). Cannabis can be categorised specifically as 'hemp' and 'marijuana', with both containing CBD but the notable difference is that marijuana contains an abundance of THC and hemp only very low percentages thereof (Oultram *et al*., 2021). Hemp or marijuana are terms often used to describe different cannabis strains, species or sub-species that can be cultivated to include varying concentrations of CBD and THC (SAHPRA, 2020a). Hemp oil is obtained through cold pressing of seeds from the cannabis plant, while CBD oil is extracted from the stalks, leaves and flowers of the cannabis plant, which contains higher amounts of CBD (DALRRD, 2021).

Figure 2.2: Medical *Cannabis* cultivars grown in the UK by GW Pharmaceuticals (Adapted from Clarke & Watson, 2002). **A** The larger inflorescence is a CBD-rich cultivar containing only traces of THC. **B** is a THC-rich cultivar containing only traces of CBD.

This study will mainly focus on the *Cannabis sativa* species, especially exploring the CBD compound.

2.4 Cannabidiol

2.4.1 Chemical properties of cannabidiol

Cannabidiol is a highly lipophilic, non-psychoactive phytocannabinoid, comprising of up to 40% of some varieties of the *C. sativa* plant (Campos *et al*, 2012). CBD was originally discovered and extracted from the cannabis plant in the 1940's, with the first synthetic CBD produced in 1965 (Pertwee, 2006). Adams *et* al (1940) extracted the CBD with ethanol by distillation under diminished pressure. The exact molecular structure was only made clear in the 1960's, many years after its first isolation and can be seen in Figure 2.3 below (Rogawski, 2021).

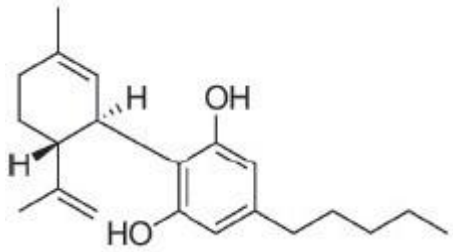

Figure 2.3: Molecular structure of cannabidiol (Rogawski, 2021).

2.4.2 Pharmacology of cannabidiol

During the 1980's, cannabinoid (CB) receptors were identified pharmacologically with two distinctive G-protein coupled receptors called CB_1 and CB_2. Although the receptors are coupled similarly, they exhibit different expression patterns (Vanderah, 2021). CB_1 receptors are found widely in many organs of the body, but mainly in the neurons of the peripheral and central nervous system (Pertwee, 1997). CB_2 receptors are found less extensively and are located primarily in the immune cells, lymph nodes, spleen, and tonsils (Pertwee, 2002).

The mechanism of action for CBD is not completely known, but it has been proposed that CBD acts as an antagonist on the central CB_1 receptor, resulting in the inhibition of several CB_1 facilitated effects, including anxiety (Grotenhermen, 2004). CBD is clinically used in the treatment of epilepsy in children associated with Lennox-Gastaut and Dravet syndrome, but the mechanism for the antiseizure activity is unknown (Rogawski, 2021). CBD exhibits anti-inflammatory properties and is also used to treat other diseases with studies showing that it can be used in anxiety and schizophrenia (Rong *et al.,* 2017).

2.4.3 Safety and tolerability of cannabidiol

There are several studies that suggest CBD is well tolerated and safe for human use in high doses and extended periods of time, however *in vitro* and *in vivo* studies indicated decreased P-Glycoprotein activity, cytotoxicity as well as potential drug

metabolism interactions. This highlights the need that additional monitoring is required in clinical practice, especially in the treatment of psychiatric disorders (Bergamaschi *et al*, 2011).

Data from clinical trials suggest that CBD is well tolerated with relatively few serious adverse side effects, with pneumonia, sedation, somnolence, and abnormal liver function tests associated with childhood epilepsy studies (Chesney *et al*, 2020). Diarrhoea was associated with other studies not related to childhood epilepsy (Schoedel *et al*, 2018). Additional safety data from clinical trials not relating to childhood epilepsy syndromes are however required to assess whether the conclusions drawn can be applied more broadly (Chesney *et al*, 2020).

Iffland and Grotenhermen (2017) extended the comprehensive search that Bermasachi *et al*. did in 2011 regarding the side effects and safety of CBD. It was confirmed that CBD has a favourable safety profile in humans and the common side effects reported were changes in weight and appetite, tiredness, and diarrhoea. Compared to other drugs used to treat epilepsy and psychotic disorders, it was found to have a better safety profile, which could improve patient compliance to treatment. Nonetheless, important toxicological parameters are yet to be studied and more clinical trials with many participants over an extended period of time are required.

2.4.4 Legal status of cannabidiol in SA and other selected countries

Cannabis and its derivatives were until recently widely restricted globally under legislation claiming that they had no medicinal value and carried the potential risk of misuse (Freeman *et* al., 2019). The legal status of CBD is very complex and controversial in many countries. In countries like the United Kingdom (UK), the US and Germany, CBD has technically been classified as a new drug for approval, demanding manufacturers to meet standards relating to quality, safety, and efficacy of any newly developed drug (Hazenkamp, 2018). In contrast, CBD has been classified as a novel food in the EU (Tallon, 2020). For this study, the EU, US, and Australia were used as a benchmark against which the South African policies will be reviewed and evaluated.

Currently in SA, CBD is considered a schedule 4 medicine, except for products with low-risk claims, containing less than 0,001% THC, a maximum dose of 20 mg CBD per day and no more than 600 mg CBD per sales pack, which is classified as a schedule 0 complementary medicine (DoH, 2019). Some of these low-risk indications include general health enhancement and relief of minor pain without reference to a specific disease, health maintenance and contribution to healthy sleep (SAHPRA, 2020b). SAHPRA (2020a) notes there are, to date, no registered cannabis containing medicines in SA and access to these medicines can be gained through the Section 21 medicines pathway. In Section 21 of the Medicines and Related Substances Act (Act 101 of 1965), provisions are made to access medicine for human use which is not registered for sale in SA. These medicines may be registered for use in other countries already or in some cases are approved for use in clinal trials (SAHPRA, 2020d).

In Australia, CBD is also regarded as a schedule 4 substance, and thus only available on prescription by a heath care professional. Access to CBD medicines is only

available through special access or authorised prescriber schemes when applied for by the clinician. The medical practitioner should be appropriately qualified or have expertise on the disease requiring the treatment, with approvals granted on a case-by-case basis. Epidyolex® and Sativex® are currently the only two CBD medicines registered on the Australian Register of Therapeutic Goods (ARTG), which is regulated by the Therapeutic Goods Administration (TGA), the medicines regulatory authority in Australia (NSW, 2021). In September 2019, the Australian Capital Territory (ACT) passed a bill to legalise the personal use of small amounts of cannabis as of January 31, 2020. The recreational use of cannabis remains illegal, with the notable exception of the ACT (ACT, 2021).

In the EU, the laws regulating the sale of cannabis and its derivatives are not harmonised. For the most part, CBD products have been classified as novel foods and are therefore illegal for sale without prior authorisation from the European Food Safety Authority (EFSA) (Tallon, 2020). The cultivation of certain cannabis varieties for hemp is granted in the EU, if they are registered in the EU's *Common Catalogue of Varieties of Agricultural Plant Species* with the condition that the THC content does not exceed 0.2% of the dried flowers of the cannabis plant (European Commission, 2000). Epidiolex® is registered with the EMA as medicinal CBD indicated for severe epilepsy in children and Sativex® oral mucosal spray containing THC and CBD (nearly 1:1), is registered in the UK for the treatment of muscle spasms in patients suffering from multiple sclerosis (SAHPRA, 2020a).

The laws in the US regarding the legal status of CBD are very conflicting, as state and federal laws relating to the medical and recreational use of cannabis and cannabinoids are often in conflict. In 50% of the states, cannabis is legal for medicinal use, 17 other states allow products containing high CBD and low THC concentrations for medical use, while the federal law does not accept the consumption of any cannabis. Epidiolex® oral solution, containing 100 mg / ml of pure CBD is registered with the FDA and marketed for medicinal use, but no other formulations containing pure CBD (Mead, 2017). The sale of CBD as a dietary supplement or food ingredient is currently prohibited by the FDA, but there is no clear quality or regulatory oversight, resulting in an uncontrolled CBD market.

2.5 Registration of medicines, health supplements and foodstuffs in SA and other selected countries.

In the past, each regulatory authority followed their own application process with the registration of medicines. Stakeholders from Europe, Japan and the US then developed the Common Technical Document (CTD), which suggests a mandatory agreed upon format for representing technical documents used during the application process in the registration of medicines and is maintained by the International Council for Harmonisation (ICH) (Jordan, 2014). Many countries, even non-ICH regions make use of the CTD format for registration of pharmaceuticals. Europe and the US are members of the ICH association, but SA and Australia are observers, therefore SAHPRA and TGA respectively follows ICH guidelines and initiatives (ICH, 2021). The aim of this harmonisation is to simplify the exchange of information between regulatory authorities and to decrease time and resources required to compile medicine registration applications in multiple countries (ICH, 2016).

Medicines, including complementary and alternative medicines are required to be registered and evaluated by the SAHPRA prior to sale in SA (Keyter *et al*., 2018). For registration of a medicine with SAHPRA, a CTD should be submitted containing full chemistry, manufacturing, and control (CMC) data as well as clinical and nonclinical data (Keyter *et al*., 2019), therefore encompassing all quality, safety and efficacy data.

A medicine can be described as ‘’any substance or mixture of substances used or purporting to be suitable for use or manufactured or sold for use in –
(a) the diagnosis, treatment, mitigation modification or prevention of disease, abnormal physical or mental state or the symptoms thereof in man; or
(b) restoring, correcting or modifying any somatic or psychic or organic function in man, and includes any veterinary medicines’’ (DoH, 2017a).

The CTD is divided into 5 modules. Module 1 is the regional administrative information, Module 2 is a summary of the dossier (quality, safety, and efficacy), Module 3 contains the quality information, Module 4 is the non-clinical study reports (safety), and Module 5 consists of the clinical study reports (efficacy). Module 1 is country or region specific, while module 2-5 are intended to be common for all regions (ICH, 2016). With the registration of complementary medicines at SAHPRA, which includes health supplements, module 5 comprising of the clinical data is not required (SAHPRA, 2020c).

Complementary medicine is defined as ‘’any substance or mixture of substances that -
(a) originates from plants, fungi, algae, seaweeds, lichens, minerals, animals or other substances as determined by the Authority;
(b) is used or purporting to be suitable for use or manufactured or sold for use –
    (i) in maintaining, complementing, or assisting the physical or mental state, or
    (ii) to diagnose, treat, mitigate, modify, alleviate or prevent disease or illness or the symptoms or signs thereof or abnormal physical or mental state of a human being or animal, and
(c) is used –
    (i) as a health supplement; or
    (ii) in accordance with those disciplines as determined by the Authority’’ (DoH, 2017b).

Health supplements are described as ‘’any substance, extract or mixture of substances as determined by the Authority, sold in dosage forms used or purported for use in restoring, correcting or modifying any physical or mental state by –
(a) complementing health;
(b) supplementing the diet; or
(c) a nutritional effect,
and excludes injectable preparations, medicines or substances listed as Schedule 1 or higher in the Act’’ (DoH, 2017b).

To distinguish between complementary medicine (which includes health supplements) and foodstuff in SA has led to confusion (FACTS, 2020b). A product is defined a foodstuff under the Foodstuffs, Cosmetics and Disinfectants Act (No. 54 of 1972) as ‘’any article or substance [except a drug as defined in the Medicines and related substances Control Act, 1965 (Act 101 of 1965)] ordinarily eaten or drunk by man or purporting to be suitable, or manufactured or sold, for human consumption and

includes any part or ingredient of any such article or substance, or any substance used or intended or destined to be used as a part or ingredient of any such article or substance''. Some products on the market are sold as foodstuffs, but does not fit the definitions thereof, for example, St. John's Wort. If it is sold on its own or added to a foodstuff with no health claims, one might think it would be regard as a foodstuff, but this ingredient would not be ordinarily eaten by a person as a foodstuff and as such, does not fit the definition of a foodstuff and become subject to the regulations of complementary medicines (FACTS, 2020b).

SAHPRA concludes that CBD as an ingredient or additive is not allowed in food and that processed hemp powder or hemp seed oil containing only naturally occurring trace amounts of CBD (≤ 0,0075%) and THC (≤ 0,001%) may be deemed a foodstuff (SAHPRA, 2020a). In section 5(1)(b) of the Foodstuffs, Cosmetics and Disinfectants Act (No. 54 of 1972), it forbids the sale of food which is ''false or misleading as regards its origin, nature, substance, composition, quality, strength, nutritive value or other properties or the time, mode or place of its manufacture''. Figure 2.4 below represents the South African regulations relating to cannabis use in food.

To handle food in SA, the premises need to have a certificate of acceptability, which can be applied for in writing at the local authority/municipality in which the premises is located (DoH, 2018). There are certain standards and requirements that the facilities on a food premises must comply with depending on the type of food handled. A nutritional analysis and shelf-life study should be conducted on the product, displaying this information on the label. Processes need to be implemented to ensure the quality and safety of the food manufactured. All staff need to be properly trained and a recognized hazard analysis and critical control point (HACCP) system should be implemented and certified (ACS consultants, 2021).

In the EU, novel foods can be classified as a food that have not been consumed in the EU before the first novel food regulation came into effect on 15 May 1997 (EC, 2021). Novel Foods must adhere to the following principles: it must be safe for consumers, properly labelled as to not mislead consumers and the novel food replacing another food must not be nutritionally disadvantageous to the consumer (EC, 2021). Before a novel food product can be marketed and consumed, it must undergo a safety assessment and authorisation. This application involves preparing a technical dossier containing manufacturing and product information.

The novel foods application includes:
Part 1: Administrative information,
Part 2: Characterisation of the novel food, technical and scientific data, encompassing all manufacturing, stability and toxicology data to name but a few and
Part 3: Annexes to the dossier (EFSA, 2016).

In the US, food is also registered at the FDA, like with medicines, ensuring that proper control and regulations are enforced including proper labelling (Grebow, 2020). Generally recognized as safe or the acronym ''GRAS'' is the designation given by the FDA that a substance or chemical that is added to food, is considered to be safe by experts and therefore is exempted from usual food additive tolerance requirements (FDA, 2019).

Food is regulated in Australia by a joint food regulation system that includes policies

and laws from Australia and New Zealand. Food Standards Australia New Zealand (FSANZ) was established under the FSANZ Act to develop government regulations generally referred to as food standards, and both governments enforce these food standards through their respective laws (DoH, 2013).

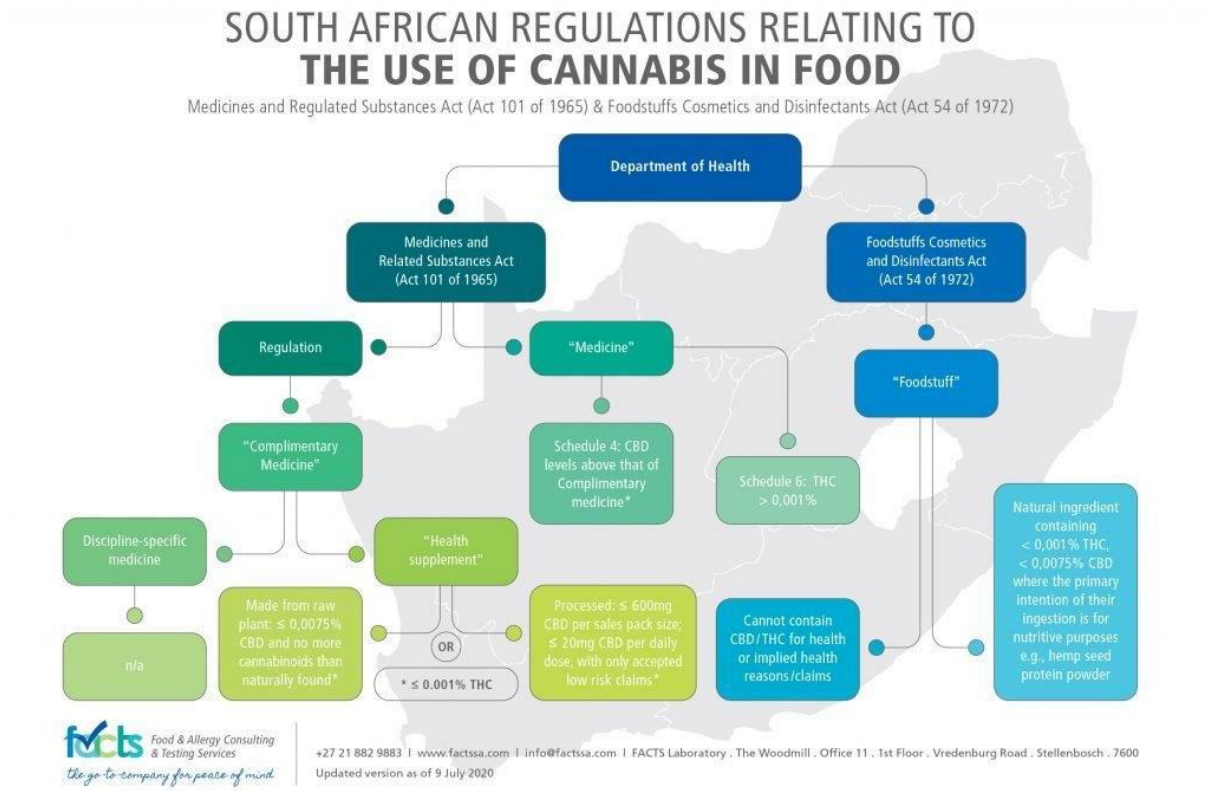

Figure 2.4: South African regulations relating to the use of cannabis in food (FACTS, 2020a).

2.6 Conclusion

It is therefore clear, through the information provided above, that CBD and the regulation thereof is complicated and very confusing for many key stakeholders, and as such, research should be conducted to get more clarity on the legal and regulatory status of CBD.

Chapter 3

Research methodology

3.1 Methodological approach

The methodological approach for this research study was a qualitative explorative method using a scoping review. Scoping reviews have gained increasing popularity and aims at mapping existing literature on a specific topic, identifying key concepts, theories, and gaps in the research (Arksey & O'Malley, 2005; Levac *et* al, 2010). Scoping reviews do not usually include a review of the quality of the literature obtained, which is a concern to some researchers, and they recommend that an evaluation of the literature should be conducted (Daudt *et al.*, 2013; Levac *et* al, 2010; Arksey & O'Malley, 2005). In this review the literature was provided without assessing the quality of each document, to ensure that no documents, reports, or literature were excluded from the study.

3.2 Methods

A systematic scoping review was conducted following the methodological framework proposed by Arksey and O'Malley (2005) and developed further by Levac *et al* (2010). The scoping review framework consisted of five stages that are listed and discussed below.

Stage 1: Identifying the research question

The research question should be well defined and focused, not too narrow, or too broad in scope to ensure that it is complex enough to allow for exploration and analysis. Originally, the intention was to review literature related to the legal status of CBD around the world, but soon realised that the topic was too broad and that every country had their own regulations and legislation with regards to CBD. The decision was made to focus on CBD regulation in SA and then to select only a few countries around the world to compare the legal status of CBD with. The other countries selected included the US, EU, and Australia. Australia was selected because they have very strict regulations regarding CBD, the EU classifies CBD as a novel food and in the US, the regulatory authority has control over both medicines and foods. The preliminary research question driving my literature search was ''How could the supply and sale of CBD and related products be regulated or controlled in the South African market?''

Keywords and search terms extracted from the research question included Cannabis, cannabidiol, policies, regulation, legal status, medicines, health supplements, foodstuff, South Africa, European Union, United States and Australia.

Stage 2: Identifying relevant literature – search strategies

An iterative process was followed to search for literature. Literature sources that were considered included any published articles, books, pharmaceutical monographs /

pharmacopoeias/ reference books / databases, pharmacology textbooks, government and regulatory agency websites, case law, reports from relevant organization and agencies and regulations that were available in the public domain. The databases used included Google Scholar and PubMed. Potential grey literature was identified searching for dissertation and theses through targeted searches. The review was conducted to compile sufficient information to ensure an extensive examination of existing sources highlighting the legal status of CBD and the introduction thereof int the South African market. The above-mentioned keywords and search terms were used in different combinations during the database search. The PubMed search was conducted using Boolean operators as shown below.

Search terms used: (cannabidiol) AND (South Africa), ((cannabidiol) AND (South Africa)) AND (regulation), ((cannabidiol) AND (South Africa)) AND (legislation), ((cannabidiol) AND (South Africa)) AND (Legal status), (cannabidiol) AND (legal status), (CBD) AND (legal status), (CBD) AND (South Africa), (cannabidiol) AND (health supplement), (CBD) AND (health supplement), (cannabidiol) AND (policies), (((cannabidiol) AND (Australia)) OR (European Union)) OR (United States).

Stage 3: Selection of relevant literature

Inclusion and exclusion criteria were determined before the start of the study to ensure that relevant literature is selected that will clarify the research question (Daudt *et al.*, 2013; Levac *et* al, 2010). Literature was selected that directly aligns with the research question.

Inclusion criteria for the literature included:

- The keywords and phrases above are included as keywords, or in the title or abstract of the document
- Literature relating to CBD products and their uses
- Literature relating to policies and regulations of CBD
- Literature relating to the registration of medicines and food / foodstuff
- Legislative and policy information from chosen countries / regions including SA, EU, US, and Australia
- Selected documents are written in English

Exclusion criteria for the literature included:

- Articles to which access could not be obtained
- Articles written in another language than English
- Literature from countries / regions not included in the scope of this study

Stage 4: Charting of the data

Literature meeting the inclusion criteria was reviewed and key information was extracted and charted into a table to allow for comparison. Some of the data extracted included: author(s), country/region, source type, journal (publication), year of publication, peer review status, study question or objective, outcomes, and author conclusions. Appendix B provides data extraction and collating system. The search strategy is shown in Appendix A, and it reports the total number of documents sorted, included, excluded and the final number of documents used.

Stage 5: Collating, summarising, and reporting of results

Results were collated and summarised in Chapter 4 and discussed and concluded in Chapters 5 and 6 respectively to assist in understanding the complex and extensive literature, answering the proposed research question and subsequent research objectives.

Optional framework stage: Consultation exercise

An optional step in the methodology to enhance scoping reviews include a consultation exercise where consumers, practitioners or other stakeholders can contribute to the review. (Daudt *et al.*, 2013; Levac *et* al, 2010). This step is not a requirement and even though it offers additional sources of information and rigor to the study, due to time constraints it was not conducted.

3.3 Ethical considerations

Due to the nature of the study and the qualitative method chosen to collect data, no ethical approval was needed from the Research Ethics Committee of the university. Data were collected using sources that were publicly available. Even though it was not required to obtain ethical approval, it was important to be mindful and conduct the research according to ethical considerations and principles, some of which include the honest reporting of data and results and to maintain research integrity.

3.4 Conclusion

A scoping review is an appropriate and effective tool to review existing literature relating to regulating the introduction of CBD products in the South African market, identifying key ideas and gaps in the literature. This chapter focused on the methodological approach that was followed to collect and analyse data, noting ethical considerations that were adhered to during the period of this study. Chapter 4 includes the results obtained during the literature search and thus the execution of the scoping review.

Chapter 4

Results

4.1 Introduction

The search, screening and selection process of the relevant records are shown in Appendix A, Search Strategy and was conducted from 24 – 31 October 2021. The keywords were used in different combinations noted in Chapter 3, with no specific parameters or limits on publication dates. A combined total of 1132 potential records were identified, with 1126 through the Google Scholar and PubMed databases, 6 additional records were identified through other sources including hand and bibliography searches or web-based grey literature. After the duplicates were removed through title screening, 855 records remained. The titles, abstracts and keywords were evaluated to ensure records met the inclusion criteria. There were 785 records excluded because they did not meet the relevant inclusion criteria, or they were unobtainable. The remaining 70 full text records were reviewed in more detail. A total of 24 documents were included in this scoping review after the final in-depth review thereof. Appendix B, the data extraction table, contains a tabulated summary of the records that were included in the study in chronological order.

The results will be presented in an overview where information regarding the articles will be given as well as the cross-cutting themes that were found. Then the results will be summarised according to the countries or regions pertaining to the scope of this study.

4.2 Overview of results

The final records included ranged in publication dates from 2017 to 2021, as this represents the most recent CBD regulations. It was found that the articles were not original or empirical research, with most being review articles of secondary data (n=17) and some commentaries (n=4). The sources of the articles included journal articles (n=20), government regulatory websites (n=2) and company websites (n=2).

Most of the records originated from English speaking countries, with the highest contributors and countries mentioned being the US and EU with 14 and 7 publications respectively. South Africa and Australia had much fewer publications, the former with 4 and the latter with 3.

The results obtained revealed a few cross-cutting themes which include firstly CBD containing products that described the uses, availability, safety, and quality of CBD containing products as well as distinguishing between products made from hemp, CBD and cannabis. Secondly and the main theme of the study, was the legislative categorisation of CBD products, that defined the regulatory and legal status of CBD containing products and the subsequent classification as a medicine, health supplement or food. Third and lastly, stakeholders involved in drafting policies and legislation regulating CBD and CBD containing products.

An overview of the cross-cutting themes is shown below in Table 4.1, specifying the intention (question or objective) of the articles found in the data extraction table (Appendix B).

Table 4.1: Summary of cross-cutting themes

Cross-cutting theme	Intention of articles	Number of articles (n=)	Reference
CBD containing products	Describing the distinction between hemp, cannabis, and CBD	2	VanDolah *et al*, 2019; SAHPRA, 2020
	Uses of CBD / products	3	TGA, 2017; Gibbs *et al*, 2019; Brunetti *et al*, 2020
	Accessibility / sale of CBD	3	Nicoletti, 2017; McGregor *et al*, 2020; Tallon, 2020
	Safety of CBD	2	Hazenkamp, 2018; Haroutounian *et al*, 2021
	Quality of CBD products	3	Hazenkamp, 2018; Gibbs *et al*, 2019; Jooste *et al*, 2021
Legislative categorisation of CBD containing products	Legal and regulatory status	17	Mead, 2017; Nicoletti, 2017; Corroon & Kight, 2018; Ebbert *et al*, 2018; Hazenkamp, 2018; Papaseit *et al*, 2018; Gibbs *et al*, 2019; Mead, 2019; O'Connor & Lietzan, 2019; Spindle *et al*, 2019; VanDolah *et al*, 2019; Brunetti *et al*, 2020; Marcu, 2020; McGregor *et al*, 2020; SAHPRA, 2020; Van Rensburg *et al*, 2020; Jooste *et al*, 2021
	Medicinal (scheduled and unscheduled)	4	TGA, 2017; Ebbert *et* al, 2018; SAHPRA, 2020; Van Rensburg *et al*, 2020
	Complementary medicine / health supplement / dietary supplement	6	Corroon & Kight, 2018; Hazenkamp, 2018; Koturbash & MacKay, 2020, SAHPRA, 2020; Van Rensburg *et al*, 2020; Cerino *et al*, 2021
	Food (novel food)/ cosmetics	6	Nicoletti, 2017; Hazenkamp, 2018; O'Connor & Lietzan, 2019; Koturbash & MacKay, 2020; Cerino *et al*, 2021;

			Walker *et al*, 2021
Participants involved in CBD policies and legislation	Policies affecting research	2	Augustine *et al*, 2018; Spindle *et al*, 2019

4.3 Summary of results per country/region

4.3.1 South Africa

The South African Constitutional Court decriminalized the private use, possession, and cultivation of cannabis in 2018. Provisions in the Medicines and Related Substances Act prohibiting the sale of unregistered CBD products were amended in 2019 by the Minister of Health, to exclude CBD products with a maximum daily dose of ≤20 mg CBD, from the schedule of medicines (Van Rensburg *et al*, 2020). These CBD products subsequently fell into the category of schedule 0 complementary medicines, while other products containing CBD are schedule 4 and any product comprising of more than 0.001% THC, is classified as a schedule 6 medicine. Schedule 0-2 medicines does not require a prescription from a doctor and can be obtained over the counter (OTC). These changes in the schedules of CBD medicines have resulted in CBD products of poor quality that are contaminated with THC as proper controls are not in place (Jooste *et al*, 2021). SAHPRA (2020a) noted that hemp and marijuana are colloquial terms commonly used to describe the different strains or species of the cannabis plant. It was also mentioned that CBD can only be regarded as a foodstuff when the concentrations of CBD and THC is less than 0,0075% and 0,001% respectively. Augustine *et al* (2018) concluded that more research on cannabis and its extracts should be conducted in SA and that the medical and scientific community, which include medical practitioners and researchers, should be involved in creating the cannabis policies for SA.

4.3.2 Australia

In Australia, the use of CBD is illegal, and a prescription is required to access any medicinal CBD product (McGregor *et al*, 2020). CBD products for medicinal use can only be obtained through special access schemes through a medical practitioner that is registered because no other CBD products, except for Sativex® (Nabiximol) is registered (from 2012) on the Australian Register of Therapeutic Goods (TGA, 2017). In 2017, the ministers approved a recommendation by FSANZ to permit the sale of hemp seed and low THC hemp seed products in food. The approved proposal included a maximum limit of 75 mg/kg CBD, with labelling and advertising that excludes the representation of the cannabis plant, the words ‘’marijuana’’ and ‘’cannabis’’, any CBD nutritional claims and any argument that the food has psychoactive effects (Nicoletti, 2017).

4.3.3 European Union

For the medicinal use of cannabis in the EU, the product needs to be registered as such and the patient requires a prescription to obtain the medicine (Gibbs *et al*, 2019;

Brunetti *et al*, 2020). Extracts of cannabis have recently been classified as a novel food, requiring a valid application to the EFSA for the products to be legally sold on the market (Hazenkamp, 2018; Brunetti *et al*, 2020; Koturbash & MacKay, 2020; McGregor *et al*, 2020; Tallon, 2020, Walker *et al*, 2021). The CBD market is subject to generic regulation, as no specific regulations or regulatory pathways have been developed for CBD. The end product category determines if the product will be regulated according to the relevant food, medicine or cosmetic regulation, with regulators and their remit not being able to overlap. CBD products used for medicinal purposes is classified as a medicine and should be licensed, otherwise it is classified as a Novel food. The due date for products to comply with this novel food's regulation was 31st of March 2021, but in some countries like the UK, the laws have not been strictly enforced yet (Gibbs *et al*, 2019). Walker *et al* (2021) note that edible CBD products should be regarded as food or food supplements and valid applications should be submitted to the FSA. Enforcement action should be taken against non-compliant companies and products. Despite early reports, the safety of CBD products is still concerning as the accumulated effect of chronic use have not been established (Tallon, 2020) and better regulatory controls should be enforced to ensure high quality CBD products that are safe and beneficial for patients to use (Hazenkamp, 2018). Gibbs *et al* (2019) concluded that all stakeholders should work with one another towards a common purpose of a CBD industry that is innovative, socially responsible and delivers high quality products.

4.3.4 United States

From most of the records obtained, the authors all note the confusing and conflicting regulation of cannabis in the US. This confusion is due to state and federal laws concerning cannabis that are different (Mead, 2017; Corroon & Kight, 2018; VanDolah *et al*, 2019; Marcu, 2020). Under federal law, the use of cannabis and any cannabis related products is illegal (Hazenkamp, 2018). Cannabis is classified as a schedule I substance meaning that it does not have any medicinal properties and has a very high abuse potential (Corroon & Kight, 2018; Mead, 2019; Brunetti *et al*, 2020). This is mostly due to the THC component found in cannabis, while the structure of cannabis has only been properly identified in recent years, showing that it contains other components including CBD. The medicinal properties of CBD have also only been recently identified, with a few clinical trials that are currently underway to prove safety and efficacy thereof. There is only one cannabis product registered (2018) in the US with the FDA to date, Epidiolex®, a product containing pure CBD (100 mg/ml) used to treat a rare form of epilepsy found in children suffering from Dravet and Lennox Gastaut syndrome (Mead, 2019). With this submission of an investigational new drug application for Epidiolex®, clinical trials in humans are currently underway, thus hemp derived CBD products can't be registered as dietary supplements (Corroon & Kight, 2018). With the implementation of the 2018 Farm Bill, the legal status of hemp derived products and its extracts was relaxed (Mead, 2019; Koturbash & MacKay, 2020). The conflicting state and federal laws regarding the regulation of CBD have led to lack of oversight by the regulatory authorities (Marcu, 2020). With these relaxed enforcements, manufacturers do not always manufacture products that comply with good quality and standards, resulting in trusting consumers buying products that might not be safe and effective for them to use. It is now also easier for manufacturers to get their products into the market without having

to conduct lengthy and expensive clinical trials to prove safety and efficacy (Haroutounina, 2021). Corroon & Kight (2018) noted that confusion also arises between the definition of cannabis and hemp and the CBD products subsequently derived thereof. Ebbert *et al* (2018) concludes that cannabis can be used by clinicians as an additional management tool in patients with debilitating symptoms. Descheduling of cannabis would ensure that CBD products can be regulated through various pathways depending on the use and research and development into cannabis and its constituents would be expected to expand (O'Connor & Lietzan, 2019).

4.4 Conclusion

The results obtained during the study showed the most recent legal and regulatory status of CBD in SA as well as Australia, the EU and US. In the last 5 years, the regulatory landscape of cannabis and CBD has changed significantly due to increased popularity and consumer demand, resulting in policy and legislative reviews with some countries making amendments to their regulations. In chapter 5 the main findings in the results are discussed.

Chapter 5

Discussion

5.1 Introduction

The aim of the study was to determine the classification and subsequent registration of CBD containing products in SA and whether the South African regulatory system is ready to effectively regulate and control the introduction of CBD in the market. The discussion will focus on the aim as well as the objectives of the study, discussing CBD containing products, regulations governing these products in SA and other selected countries, stakeholders in legislation and possible considerations for stakeholder development that emerged during the execution of the study. The limitations of the study will also be considered at the end of this chapter.

5.2 CBD containing products

A major finding in the results were the ambiguity between hemp, CBD, and cannabis and the resulting CBD containing products. All three are from the same genus and species, *Cannabis sativa*, but due to domestication of the plant, various strains with different concentrations of CBD and THC have evolved. This could be one of the reasons contributing to the confusion of the general public that perceive that they are the same and can be used interchangeably (Oracle, 2022). However, there are clear distinctions between the three, which are very important especially when it comes to the intention and outcome of their use. Hemp is a certain cannabis strain that contains low concentrations of THC, which is mainly used as a source of food and fiber for other industrial uses (Cerino *et al*, 2021). CBD is also found in the cannabis plant but is extracted from specific strains that contain high concentrations of CBD and relatively low THC concentrations. Cannabis is colloquially referred to as marijuana, which contains high concentrations of THC and low concentrations of CBD and is typically smoked to get the psychoactive effects of THC (SAHPRA, 2020a).

The results of this scoping review found that there are many CBD products available on the market worldwide, ranging from products used for recreational purposes to nutritional and medicinal uses (Nicoletti, 2017; Therapeutic Goods Administration, 2017; Augustine *et al*, 2018; Ebbert *et al*, 2018; Gibbs *et* al, 2019; Mead, 2019; O'Connor & Lietzan, 2019; VanDolah *et al*, 2019; Brunetti *et al*, 2020; Cerino *et al*, 2021). CBD products containing high levels of THC are predominantly used for recreational purposes as part of social, cultural, or religious traditions and are administered mainly through inhalation (smoking or vaporising) relying on the psychoactive properties of THC (DALRRD, 2021). Nutritional and medicinal benefits are mostly associated with products containing higher concentrations of CBD and low concentrations of THC and are used for treatment or alleviation of various diseases or symptoms.

The results also showed that in some countries like Australia, CBD products are not allowed to have any representation of the cannabis plant, whether pictures or words and accurate labelling and advertising is regulated (Nicoletti, 2017). Some CBD products are also incorrectly presented as originating from hemp and not cannabis, but

hemp (which is legal) usually contains very low levels of CBD, and as a result, the products are mostly fortified with CBD to increase the concentration thereof (Pistilli, 2019). Both these misrepresentations could be due to CBD products trying to distinguish themselves from THC products, which is highly regulated and coupled to the social stigma that cannabis is incompatible with social expectations (Reid. 2020). Several studies conducted on CBD oils and cannabis products worldwide have shown that products contain contaminants (including chemicals, solvents and pesticides) and incorrect or misleading label information, which is a direct result of the unclear legal status of CBD or proper agreement on implementation of general quality and safety standards (Hazenkamp, 2018).

5.3 CBD policies and regulation

One of the recurring themes in the results is the difference between what constitutes a medicine and what is considered a food. Hazenkamp (2018) noted that the main difference between a medicine and a natural food is that the latter is generally considered safe until proven unsafe, while medicines are believed to be unsafe until proven safe. This leads to the key question whether CBD is considered a food, medicine, or health supplement.

In the literature review, it was mentioned that in SA a food is defined as any substance that is ordinarily eaten or drunk by a person except if it falls under the definition of a medicine (Foodstuffs, Cosmetics and Disinfectants Act No. 54 of 1972). A medicine is any substance used to diagnose, treat or prevent a disease and a health supplement is any substance that has a nutritional effect, complements health or supplements the diet and both are regulated under the Medicines Act (DoH, 2017a). Therefore, the difference between a health supplement and a food is that the former makes health claims, even if it is low risk claims, while foods are not allowed to make any health-related claims.

CBD is considered either a medicine, health supplement or food in SA, depending on the dose of CBD, pack size, THC concentration and health related claims, meaning that it can be classified as schedule 6, 4 or 0 (OTC) medicines. It seems the famous dictum of Paracelsus is applied when it comes to CBD stating ‘’What is there that is not poison? All things are poison, and nothing is without poison. Solely the dose determines that a thing is not a poison.’’ (Grandjean, 2016). In other words, regulation of CBD in SA is completely dependent on the dose of the product. Currently, there are no schedule 4 or 6 CBD containing products registered in SA (SAHPRA, 2020a), therefore the only CBD containing products available are schedule 0 and classified as complementary medicines (in the category of health supplements) (SAHPRA, 2021). This approach is similar to what is done in Australia, where the classification is based on the concentration of the CBD present in the product (TGA, 2017).

CBD containing products can only be regarded as foodstuffs (not including food supplements) in SA, when it only contains naturally occurring trace amounts of CBD (≤ 0,0075%) and THC (0,001%), does not contain whole cannabis seeds and no health benefit claims are made. Examples of these include hemp seed oil and hemp protein powder (SAHPRA, 2020a). However, a simple search on the internet for CBD containing products, revealed multiple results advertising food products such as

coffee, tea, water, and chocolates, with a purported CBD content of up to and more than 10 mg per serving, which is significantly above the allowable limits for foodstuffs. Furthermore, medicinal benefits are also claimed, clearly shifting the product into the realm of a medicine or health supplement. Thus, the unregulated use of CBD in certain food and beverages is widespread in SA without apparent enforcement of above-mentioned regulations. It is important to note that this lack of enforcement should not be interpreted as making the products legal.

The regulation of CBD in food in SA is made difficult by the fact that food and their subsequent ingredients, are not held to the same quality standards as opposed to the components or raw materials used in medicines. Food products are regulated by the Foodstuffs, Cosmetics and Disinfectants Act (No. 54 of 1972) prohibiting the sale of food which is ‘’false or misleading as regards its origin, nature, substance, composition, quality, strength, nutritive value or other properties or the time, mode or place of its manufacture’’. However, no provisions for regular testing and quality control are made. The CBD active used in medicines must conform to strict purity standards, especially in terms of the amounts of THC that are allowed to be present. The implication of inadequate quality control in the food industry means that impurities and THC may be found in products containing CBD used in food.

It can clearly be seen that this is not the case for the EU and the UK, where the novel foods application requires data including comprehensive quality, safety and efficacy reports supporting the use as a food (EFSA, 2016). Still, enforcement of regulations is problematic. In the US, both food and medicines are regulated by one regulating body, namely the FDA, supposedly ensuring proper regulation and control of both. However, currently CBD is not permitted in food or dietary supplements by the FDA, but is allowed by nearly half of the states, contradicting the FDA’s current position that CBD is illegal in foods, beverages, and dietary supplements (Grebow, 2020). CBD in food is not permitted in Australia at this time, although the government has approved the recommendations from FSANZ allowing the sale of low THC hemp seed products in Australia (Nicoletti, 2017).

5.4 Stakeholders for CBD legislation in South Africa

In the cannabis industry, there are several stakeholders that need to give their input and need to be included when the CBD legislation is being developed. The results of this study showed that the main stakeholders in the CBD market included the retailers, manufacturers, regulators and policy makers (Gibbs *et* al, 2019). In the US, the department of Agriculture was involved in either confusing legislation or adding to its complexity (Corroon & Kight, 2018; Mead, 2019 Koturbash & MacKay, 2020). However, in SA, the government decided that a national strategy is required for the industrialisation and commercialisation of cannabis, and DALRRD was appointed as the convenor of this process. Representatives of various departments form this committee which includes the Departments of Health, Justice, Small Business Development, Science and Innovation, Trade, Industry and Competition, the South African Police Service as well as the Presidency. Other representatives include the Agricultural Research Council, SAHPRA, Centre for Scientific and Industrial Research, and some universities (DLARRD, 2021). To cultivate and grow cannabis for commercial purposes in SA, the cultivator needs to be registered with SAHPRA,

and have a licence (SAHPRA, 2017).

5.5 Possible considerations for legislation development

The primary gap is the quality assurance for CBD products used in food and health supplements including raw materials used, extraction process of the CBD, formulation and finished products. A first step in implementing regulatory standards would be to demand proper and accurate labeling, ensuring that all raw materials used are listed and that the product is analytically tested and released based on a certificate of analysis (CoA). For the extraction of CBD, a recognised monograph should be followed to extract the CBD from the specific allowable stain of the cannabis plant. This would start to ensure the quality and safety of the product, showing that it does not contain THC and other contaminants. For CBD used in food products, using only CBD from licensed manufacturers that can provide a CoA, should be allowed, once again providing assurance of THC and contaminant free products.

The South African government is in the process of developing a national cannabis master plan which was presented in August 2021 but was challenged by industry, researchers and experts in the cannabis sector, the department of Social Development, Higher Education and Training, the National House of Traditional Leaders as well as some others. Major concerns raised included challenges obtaining licences, confusion regarding hemp permits, high entry barriers, illegal products on the local markets, inclusion of dagga growers and traders as part of the cannabis industry and the roles each province must play, which has led to the master plan being rewritten (DLARRD, 2021). It is commendable that the government is trying to address key challenges that were identified and to grow and develop the cannabis industry in SA.

5.6 Limitations of the study

Some limitations were encountered while conducting the scoping review. With the problem statement and research question chosen, it is difficult to search for literature using the conventional databases including PubMed, as some of the information is not from studies conducted, but rather government and regulatory agency documents and reports. The records and results obtained provide an indication of what is currently available, but the CBD market is rapidly expanding. As such, this analysis regarding regulations and policies may quickly be superseded with changes issued by government and regulatory authorities. The shortage of clinical trials research on the therapeutic benefits and possible side effects on the short- and long-term use of CBD is negatively impacting the scientific foundation regulations are based on.

Chapter 6

Conclusion and future recommendations

6.1 Study conclusions

This study found that South Africa was not ready, but rather in the process of developing legislation that would properly introduce CBD into the market. CBD can be classified as either a medicine, health supplement or food in SA based on the concentration of CBD in the product. No schedule 6 or 4 containing CBD products are currently registered in SA and only trace amounts of CBD are allowed in food products (officially), which means in practical terms only schedule 0 complementary medicines (open shop/OTC) CBD products are available to the South African public. However, it is clear that CBD containing food products are becoming widely available on the market in apparent contravention of the regulations and is thus not adequately regulated and controlled due to the failure to enforce the proposed regulations. If not enforced, the best regulations are ineffective.

It can clearly be seen from the literature that the cannabis and specifically the CBD industry is very complex and evolving. The legal status of CBD differs from country to country and there are not clear and harmonised regulations. More concerning is the existence of contradictory legislation from different regulatory authorities within one country, such as the USA. The current legislation and regulations governing CBD in medicines, but also in food, is not adequate and appropriate for the local and international markets. The legal status of CBD products depends mainly on their overall composition. The 'greyness' of the regulations can be attributed to the presence of THC, which is regarded as a controlled substance and not permitted under criminal law.

Limitations of this study include that the problem is very wide and complex, making it difficult to have an exact starting point, the regulations are subject to change and regulations vary from country to country and even in a country from region or state to state.

6.2 Future research

More research should be conducted on the purity of products on the market, which is directly related to the quality of the raw materials used during manufacturing. This would give an indication if the raw materials used were free of contaminants and that the manufacturing process complies to quality standards.

Additional clinical data should be compiled to better understand the potential therapeutic benefits and indications with the use of CBD, but also to identify the purported safety profile thereof. The chronic use of CBD and the accumulative effect on the body have not yet been properly investigated. With the high demand and popularity of CBD and its subsequent products growing exponentially, it's important that this information be obtained as soon as possible and investment in clinical trials made.

6.3 Recommendations for practice

The development, success, and sustainability of the CBD market in SA depends on overcoming certain key challenges. I propose a framework where all stakeholders including the industry (growers, manufacturers, sellers), healthcare professionals, regulators, and government should work together to develop policies and regulations that is in the interest of the public or consumer, ensuring that high quality products are delivered that is safe and effective. The CBD market can be a source of great income for a country and have many therapeutic benefits, but it should be regulated correctly.

Better definitions of CBD, hemp and cannabis should be developed, registration of cannabis strains should be enforced to ensure that the subsequent extracts or products is regulated accordingly. Campaigns should be implemented to inform the public about what CBD is, what potential benefits it has but also the potential side effects it can exhibit. The stigma associated with terms like dagga, marijuana, weed and grass which refers to THC and its psychoactive effects, negatively impacts on all aspects of CBD including research, development, clinical trials, regulation, marketing, cultivation and distribution. Although a better understanding of the differences between the substances is emerging, ongoing public education and information campaigns are important.

It is thus recommended that in SA, CBD can be used in medicines under the current regulations, but that it can also be used in the food and beverage industry as a food or dietary supplement, if the appropriate and correct pathways are followed and regulations are enforced. Legislation should be adjusted to allow CBD to be used as food, at certain doses and if no medicinal claims are made. The supplier of the CBD substance or active should be approved through appropriate supplier quality assurance, to ensure that it is of high quality, free from impurities and that THC is absent or at the approved limits. Thus, ensuring that the substance is GRAS in terms of its intended use, no pun intended.

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Appendix A

Search Strategy

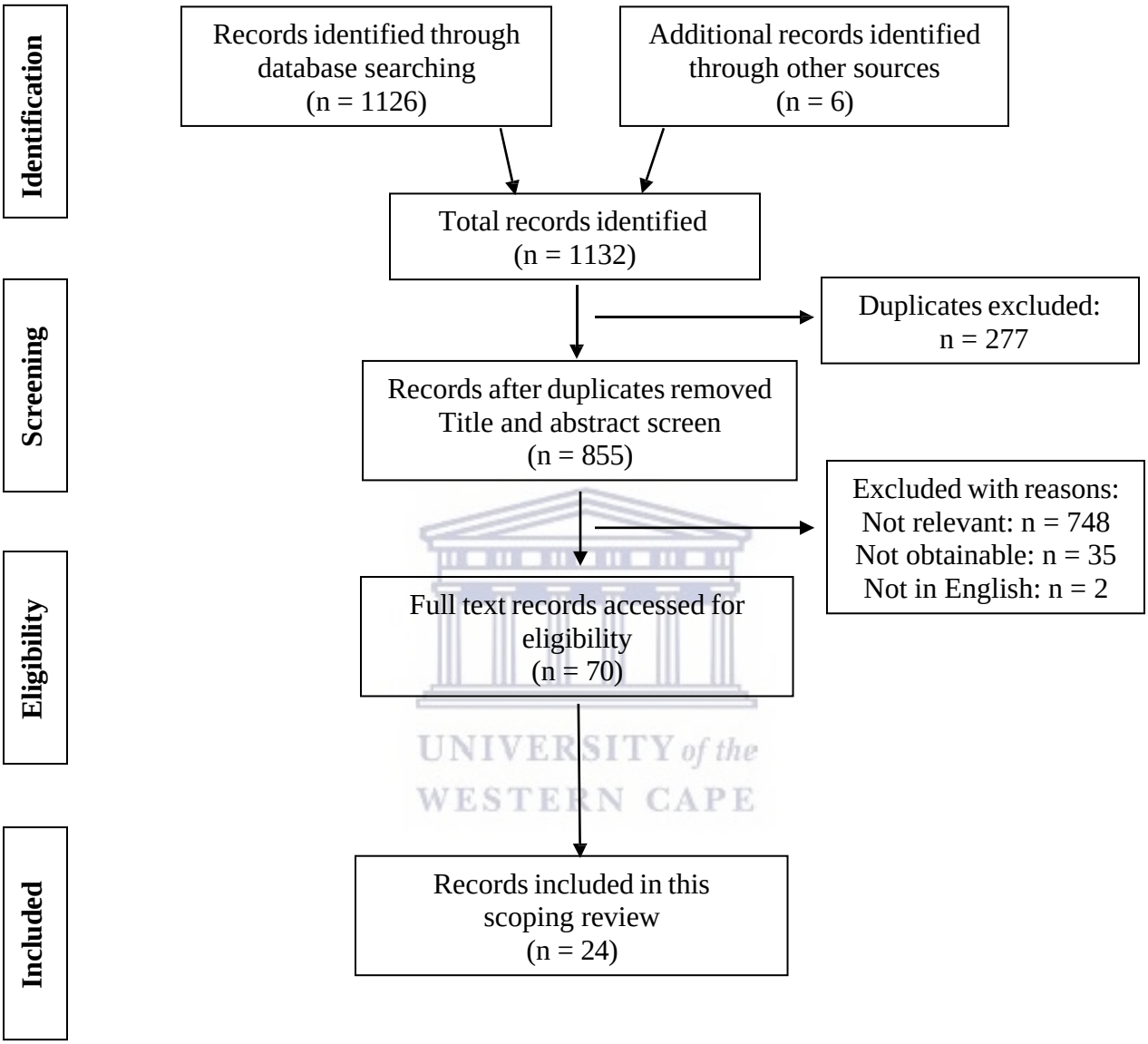

Figure A.1: Flow chart of literature/record selection process

Appendix B

Data Extraction Table:

Author(s) & country/ region:	Year:	Peer-reviewed	Source type & journal (publication):	Title:	Question or objective:	Outcomes:	Author conclusions:
Mead, A.J.D. United States	2017	√	Review article Epilepsy & Behavior	The legal status of cannabis (marijuana) and cannabidiol (CBD) under U.S. law	Understanding of federal laws can be challenging and complex, resulting in confusion regarding the legal status of CBD. This review provides an up-to-date overview of the legal aspects of cannabis and CBD.	Cannabis is legal for medical purposes in 50% of the states, another 17 allow high CBD and low THC products for medical use. CBD products available online and in dispensaries, without FDA approval.	Conflict between state and federal laws regarding the use of CBD has caused a lot of confusion for researchers, patients, and healthcare providers.

Nicoletti, T. Australia	2017	X	Commentary Mills & Oakley website	Hemp-based foods to be legalised in Australia	The sale of foods from low THC hemp seeds and hemp seed oil was approved, but other legal challenges remain, which are further explored.	The ministers approved a recommendation by the FSANZ to permit the sale of low THC hemp seeds and hemp seed products as foods. However, cannabis is listed as a prohibited plant on the food standard code. The approved proposal include: Maximum limit CBD of 75 mg/kg. Labelling and advertising prohibits representation of the cannabis plant, the word ‘’cannabis’’ or ‘’marijuana’’, nutritional claims of CBD and the representation that the food has psychoactive effects.	The Poisons Standard scheduling of cannabis and THC prohibits the use of any non-medical hemp products and states a limit of 50 mg/kg of cannabinoids, including CBD and THC in all hemp products. These restrictions are in conflict with the FSANZ, and regulations should be amended if hemp foods are to be sold legally in Australia.

Therapeutic Goods Administration Australia	2017	X	Government document (Regulatory Authority) Government website	Guidance for the use of medicinal cannabis in Australia – Patient information	To provide guidance to patients on the use of medicinal cannabis in Australia.	Except for Sativex® (Nabiximol), no other cannabis products are registered in Australia for medical use. Unapproved medicines can be accessed through special pathways through medical practitioners.	More research is required to explore the limitations, safety concerns and potential benefits of cannabis, including cannabinoids and cannabis extracts, for medicinal purposes.
Augustine *et al* South Africa	2018	√	Review article African Journal of Primary Health Care & Family Medicine	Priority areas for cannabis and cannabinoid research in South Africa	What are the priority areas for cannabis and cannabinoid research in SA?	Conduct national, multisite clinical trials, support exploratory research of the current use of extracts and conduct evaluations on the possible barriers and facilitators to prescribing cannabis, should it be legalised in the future?	It is important that the medical and scientific community be involved in developing the cannabis policies in SA as confusion exist between recreational and medicinal use, the legal status of recreational and medicinal possession and use and lastly scientific versus anecdotal evidence supporting efficacy in some medical conditions.

Corroon & Kight United States	2018	√	Perspective Cannabis and Cannabinoid Research	Regulatory Status of Cannabidiol in the United States: A Perspective	Arguments are made that the legal status of CBD is based on its source (cannabis plant or hemp), with the resulting future regulatory status of CBD that is difficult to predict.	CBD is currently listed as a schedule I controlled substance. CBD can be extracted form cannabis or hemp. Hemp-derived CBD products can currently be bought as dietary supplements. With the submission of Epidiolex® as an investigational new drug, CBD can't be included as a dietary supplement. Industrial hemp cultivated as part of the 2014 Farm Bill under the state program is legal.	Current regulatory and legal status of CBD is complex and evolving. There is confusion regarding the definitions of cannabis and hemp and the subsequent derived CBD products. The FDA's position regarding CBD as a drug and not a dietary supplement is unclear. Clinical research restrictions due to its schedule I status, have impeded the understanding of safety and efficacy considerations of CBD.

Ebbert *et al* United States	2018	√	Review article Mayo Clinic Proceedings	Medical Cannabis	Provide an overview of the legal status, pharmacology and other factors of medical cannabis as clinicians are increasingly asked by patients about medicinal cannabis.	30 US states have programmes that authorises the use of cannabis for certain medical conditions. Cannabis is illegal under federal law, requiring health professionals to be registered to certify patients for cannabis use.	Through the medical cannabis law, clinicians can provide selected patients with cannabis as an additional tool to manage disabling symptoms, where medical cannabis are mainly allowed for use in chronic pian, severe nausea, Alzheimer disease, sclerosis and cancer to name a few.
Hazenkamp, A. European Union (Netherlands) & United States	2018	√	Commentary Medical Cannabis and Cannabinoids	The trouble with CBD oil	There are many uncertainties regarding the legality, quality, and safety of CBD despite the growing availability thereof. Is CBD a food supplement, an investigational new medicine, or a narcotic?	Cultivation of cannabis varieties in the EU is allowed if they are registered. CBD enhanced natural hemp extracts are classified as novel foods. In the US many states have introduced cannabis laws, while under federal law it is illegal.	Better regulatory controls are required to ensure that CBD products are safe and of the desired quality. Clinical trials need to be conducted to ensure the efficacy of CBD as it is used by many patients and consumers for epilepsy, anxiety, schizophrenia, cancer and Parkinson's disease.

Papaseit *et al* European Union & United States	2018	√	Review article International Journal of Medical Sciences	Cannabinoids: from pot to lab	Review novel aspects of cannabis and cannabinoids in relation to their legal status	In the US, medical cannabis use is legal in 29 states and recreational use is legal in 7 states. In Europe, therapeutic use of cannabis is only legal in the Netherlands (products containing different concentrations of THC and CBD can be smoked or drank as an herbal tea), Germany and Italy.	The use of cannabis and mainly cannabinoids has increased in the recent years and has opened the debate on legalisation of recreational and medicinal use thereof.

Gibbs *et al* European Union (UK)	2019	X	Policy paper Centre for Medicinal Cannabis	CBD in the UK. Towards a responsible, innovative and high-quality cannabidiol industry	Information document regarding CBD in the UK covering the following aspects: hype, compound, law, regulations, consumer, market, industry, test, future, challenge, ask and next steps.	CBD products for medicinal purposes must have a product licence. The EU classified CBD and all cannabinoids (regardless of origin, although interpretation and applicability to natural hemp is being disputed) as a novel food but have not yet been enforced in the UK. Generic regulations govern CBD and depending on the end product and its use, it is either classified as a medicine, food or cosmetic and regulated as such.	All stakeholders including policy makers, regulators, manufacturers and retailers should work together towards a common goal a high quality, socially responsible and innovative CBD industry.

Mead, A.J.D. European Union (UK)	2019	√	Review article Frontiers in Plant Science	Legal and Regulatory Issues Governing Cannabis and Cannabis-Derived Products in the United States	The regulatory and legal frameworks surrounding cannabis in the US is discussed.	CBD is classified as a schedule I drug however the 2018 Farm Bill has descheduled hemp, as a result, commercial activity of hemp and its extracts is lawful. The FDA prohibits unregistered CBD products for medicinal use. CBD can't be sold as an ingredient in food or dietary supplements.	The social acceptability of cannabis has increased around the world. With the success of Epidiolex®, hopefully more manufacturers will bring other cannabis derived products through the FDA process, providing more treatment options to patients.

O'Connor & Lietzan United States	2019	X	Review article American University Law Review	The Surprising Reach of the FDA Regulation of Cannabis Even After Descheduling	To look at how the FDA will approach the regulation of medical cannabis, three possible regulatory pathways that can be followed in the event of descheduling.	1. Medicine: Any product containing CBD with medical claims is deemed a drug. 2. Food: Cannabis of an extract presented as a single ingredient would not qualify as a food. The FDA interprets food as any item consumed for the aroma, taste or nutritional value. Foods cannot contain drugs due to the drug exclusion rule and CBD as a single ingredient would deem it a food additive, which requires premarket approval. Additionally, no claims about CBD are allowed. 3. Dietary supplement: Dietary supplements may not lawfully contain CBD or THC due to the dug exclusion rule. A premarket notification to the FDA is required resulting from premarket safety testing. No disease or health claim may be made.	All three pathways should be available after the descheduling of cannabis. With the approval of Epidiolex, it is expected that smaller companies would invest in research and development of cannabis constituents.

Spindle *et al* United States	2019	√	Review article Current Opinion Psychology	Changing landscape of cannabis: novel products, formulations and methods of administration	This review describes emergent cannabis products, formulations and methods of administration.	Laws regulating cannabis has changed drastically in the US and other countries. Cannabis is legal for medicinal purposes in 33 states and recreational (smoked, vaporised and orally ingested) purposes in 10 states. Psychologists play an important role in studying health impact of legalisation of CBD and research on regulation of products.	Policy-orientated research and proper regulatory oversight could improve quality of products and maximise public health benefits and reduce risks.

VanDolah *et al* United States	2019	√	Review article Mayo Clinic Proceedings	Clinicians' Guide to Cannabidiol and Hemp Oils	Overview of current legal status of CBD and hemp oil in the US as well as the distinction between hemp, marijuana and different components of CBD and hemp oil products.	Legal landscape of CBD complex because of differing federal and state laws. Lack of regulation for CBD production and distribution. Differences between hemp, CBD and cannabis oils are as follows: Hemp – Extracted from the seeds of the hemp plant with no THC, little to no CBD and used as a nutritional supplement or fiber. CBD oil – Extracted from the flowers and leaves, with < 0.3% dry weight THC, high levels of CBD and used for medicinal uses of CBD. Cannabis oil – Extracted from flowers and leaves of plant, containing > 0.3% THC of the dry weight, low levels of CBD (10-15%) and used for THC effects.	CBD and hemp oil are used by patients even if it is not FDA approved. Clinicians should inform patients about the possible therapeutic benefits of CBD, including use for chronic pain, spasticity, nausea, vomiting and sleep disorders, and any safety issues that may include decreased appetite, drowsiness and diarrhoea.

Brunetti *et al* United States & European Union	2020	√	Review article Ann Ist Super Sanità	Pharmacology and legal status of cannabidiol	Focus on pharmacology and legal status of CBD and highlighting the lack of international regulatory harmonization.	In the US, hemp was removed as a schedule I substance and is legal if hemp is produced under the federal law. CBD products are excluded from any dietary supplements. In the EU, CBD products for medicinal use (claiming health benefits) requires authorisation from the EMA and other products containing CBD not for medicinal use, requires novel food authorisation.	The legal status of CBD in different counties around the world are not clear or harmonized. Legislative acts governing food, drugs and cosmetics containing CBD are inappropriate to support the current local and international markets.

Koturbash & MacKay United States	2020	√	Review article Journal of Dietary Supplements	Cannabidiol and Other Cannabinoids: From Toxicology and Pharmacology to the Development of a Regulatory Pathway	Is CBD only allowed as a drug or can it be listed as a dietary supplement and food ingredient?	The federal status of hemp derived CBD products were relaxed by the 2018 Farm Bill, bringing the regulatory status of CBD as dietary supplement into focus. In Europe, the regulation of CBD in food and medicines is becoming a main focus point, with its recent classification as a novel food.	There are many questions that needs answers. The authors propose a stewardship programme for CBD manufacturers and products where quality is the main goal.
Marcu, J United States	2020	√	Commentary Dialogues in Clinical Neuroscience	The legalization of cannabinoid products and standardizing cannabis-drug development in the United States: a brief report	Recent advances in cannabis regulation and drug approval are explored.	With the approval of Epdiolex® from the FDA, CBD was descheduled, while THC is a schedule I substance with no accepted medicinal benefits.	The lack of regulatory oversight, due to the conflict between federal and states laws, has left a huge gap in the cannabis market relating to product quality and patient safety.

McGregor *et al* Australia	2020	√	Review article International Journal of Drug Policy	Access to cannabidiol without a prescription: A cross-country comparison and analysis	Compare availability of CBD products and the associated legislative and regulatory background in nine selected countries.	Australia – prescription required to access any CBD product. USA – Federal and state legislation determines availability of CBD. CBD available online and over the counter. UK (EU) – CBD products classified as novel foods	Approaches in management of CBD differs in many countries. In some countries, like Canada, CBD fits into legislation regarding medicine, food and controlled drugs, as all CBD containing products fall under the *Cannabis Act* and stringent controls apply. In other countries, like the US, legal status is confusing and contradictory.

SAHPRA South Africa	2020	X	Government document (Regulatory authority) Government website	Cannabis and related substances	Frequently asked questions to the regulator relating to cannabis and its related products.	Hemp and marijuana are terms used to describe different species or strains of the cannabis plant. According to the medicine Act: THC is schedule 6, CBD is schedule 4 except products containing s maximum daily dose of 20 mg CBD with low-risk claims, or processed products with not more than 0,0075% CBD and 0,001% THC. Processed products containing less than the previous mentioned amounts of CBD and THC are allowed to be regarded as foodstuffs. Hemp seed oil is excluded from the medicines act depending on the concentrations of the CBD and THC concentrations. There are no cannabis containing medicines registered to date in SA.	The registration and regulation of cannabis containing medicines in SA is the responsibility of SAHPRA. CBD products that are excluded from schedule 4 is available for general sale (schedule 0).

Tallon, M.J. European Union (UK)	2020	√	Review article Journal of Dietary Supplements	*Cannabis sativa* L. and Its Extracts: Regulation of Cannabidiol in the European Union and the United Kingdom	Understanding the laws governing the sale of CBD and the challenges consumers face.	In the UK CBD is classified as a novel food requiring a valid novel food application and authorisation before marketing.	The safety of CBD products remains a concern as there is a significant gap in the safety data for chronic use, despite early reports demonstrating the safety thereof.
Van Rensburg *et al* South Africa	2020	√	Review article South African Medical Journal	Medical cannabis: What practitioners need to know	The legal and regulatory framework regarding cannabis and CBD use in South Africa is discussed.	In 2018, the SA constitutional court decriminalised the private cultivation, possession and use of cannabis. Provisions in the medicines and related substances act prohibits the selling of unregistered CBD products. In 2019, this act was amended to exclude from the schedule of medicines CBD products with a maximum daily dose of ≤20 mg CBD, with these products considered to be complementary medicines.	Regulatory oversight is required to ensure CBD products that are of high quality, safety and efficacy.

Cerino *et al* European Union	2021	√	Review article Cannabis and Cannabinoid Research	A review of hemp as food and nutritional supplement	Regulatory aspects are reviewed with regards to hemp (various parts of the plant) being consumed as a food and nutritional supplement.	Currently CBD is marketed as hemp derived dietary supplement subject to changing regulation as well as a drug such as Epidiolex® and Sativex® (Nabiximol). CBD is widely available and used despite regulatory confusion and lack of stringent controls.	The use of hemp in the food and supplement industry is expected to grow, therefore regulatory interventions are required to encourage clinical research to provide accurate safety data of these products.
Haroutounian *et al* United States	2021	√	Review article Pain®	Societal issues and policy implications related to the use of cannabinoids, cannabis, and cannabis-based medicines for pain management	Unregulated manufacturing, supply and access to cannabis can result in societal risks and harm that are reviewed.	There is an inconsistent and unregulated cannabis supply. Freedom to sell cannabis without proof of safety and efficacy gives manufacturers little motivation to conduct expensive trials. Advertising of cannabis lack regulation, resulting in false perceptions of safety.	Strict policies should be adopted to ensure cultivation of quality products, minimising harm. Advertising should also be strictly controlled to mitigate societal harms.

Jooste *et al* South Africa	2021	√	Review article South African Medical Journal	The implications of the use of cannabidiol-related products in a safety-sensitive drug testing environment: A medical-legal perspective	Lack of resources for SA to maintain legislation, has led to CBD products being sold by manufacturers that does not comply to legislative standards and contain higher concentrations of THC that are allowed.	CBD containing products are classified as follows according to the schedules of medicine: - products containing more than 0.001% THC is schedule 6 medicines - CBD products are classified as schedule 4 except products containing less than 600 mg CBD per sales pack, with a daily dose of 20 mg CBD which is classified as a schedule 0 complementary medicine. For schedule 0-2 medicines, no prescription is required.	The recent CBD changes in the schedules of the medicines act has resulted in poor quality control of CBD products.

Walker *et al* European Union (UK)	2021	X	Review article Journal of the Association of Public Analysts	Cannabinoids – a Tutorial Review. Psycoactivity, Regulation, Common and IUPAC Nomenclature, Structures and Abbreviations in Relation to Cannabidiol (CBD) Products.	Various components of cannabis and CBD are reviewed together with advancements in CBD regulation as a novel food.	CBD products may be placed on the UK market under the Novel Food Regulation if a novel food application was submitted.	CBD edible products should be regarded as food or food supplements and have valid applications at the Food Standards Agency. Surveillance and enforcement action should be made against non-compliant products.