CANNABIDIOL: SCIENCE, MYTHS AND REALITIES

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To my beloved parents, without

whom none of this would

have been possible.

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Abstract

The cannabis plant has more than one hundred cannabinoids. The two most researched cannabinoids are tetrahydrocannabinol (THC) and cannabidiol (CBD). The aim of the study was to investigate the science, myths and realities related to CBD by (i) comparing the potential therapeutic benefits of CBD (ii) assessing knowledge and perception of the public and healthcare professionals (HCPs) about CBD. Systematic literature review about studies demonstrating potential therapeutic benefits of CBD was carried out followed by the development, validation and dissemination of two questionnaires targeting the knowledge and perception of the general public and HCPs about CBD. The questionnaires consisted of 4 sections: Demographics, Knowledge, Perception and Barriers related to CBD use. One hundred and twenty-six articles were identified via systematic literature search. CBD was reported to have beneficial effects on mental health disorders (33), inflammation (27), neurological disorders (21), cancer (15), cardiovascular disease (11) and pain (6). CBD demonstrated neuroprotective effects (5) and other therapeutic effects (8). Four hundred individuals (62% female, 41% aged 26-40 years) answered the general public questionnaire and 150 individuals (58% female, 53% aged 26-40 years, 49% pharmacists) answered the questionnaire for HCPs. Seventy five percent of respondents from the general public (n=257) heard about CBD from social media/news, 79% (n=314) believe that CBD has an analgesic effect, 50% (n=202) think that CBD products should be prescription-only-medicine and 69% (n=277) disagree that CBD is a gateway drug. Sixty-five percent (n=262) of the general public respondents deemed social stigma as a barrier to CBD use. Seventy percent (n=97) of HCPs heard about CBD from social media/news, 67% (n=101) believe that CBD products should be prescription-only medicine, 69% (n=104) would feel comfortable in prescribing or recommending CBD for pain, 61% (n=91) of HCPs disagree that CBD is a gateway drug

and 65% (n=97) of HCPs deemed their personal beliefs as a barrier to CBD use. Publications reported therapeutic effects of CBD. Members of the general public (79%, n=314) and HCPs (97%, n=145) perceive that CBD has an analgesic effect. CBD is a naturally occurring compound derived from cannabis that has beneficial and therapeutic effects and also adverse effects. This study demonstrates that participants from the general public aged between 18-25 years and having a tertiary level of education were more knowledgeable about CBD than other age groups yet healthcare professionals agree that there is a lack of education and misconceptions among the general public about CBD and its use in medical conditions. Healthcare professionals and the general public perceive that CBD products should be prescription only medicine. Two common barriers related to CBD use are social stigma and negative personal beliefs of HCPs.

Keywords: cannabidiol, therapeutic benefits, questionnaires, systematic literature search

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List of Abbreviations

2AG – 2-arachidonoylglycerol

AD – Alzheimer's disease

ALT – Alanine transaminase

ALS – Amyotrophic lateral sclerosis

ANA – Anandamide

AST – Aspartate aminotransferase

cAMP – Cyclic adenosine monophosphate

CB – Cannabinoid

CBD – Cannabidiol

CHR – Clinical risk of psychosis

CNS – Central nervous system

COX – Cyclooxygenase

DBP – Diastolic blood pressure

DRG – Dorsal root ganglion

DS – Dravet syndrome

EAE – Experimental autoimmune encephalomyelitis

EAM – Experimental autoimmune myocarditis

EGF – Epidermal growth factor

EGR2 – Early growth response 2

EMA – European Medicines Agency

ERK – Extracellular-signal-regulated kinase

EU – European Union

FDA – Food and Drug Administration

FIP – International Pharmaceutical Federation

FREC – Faculty Research Ethics Committee

GABA – Gamma-aminobutyric acid

GFAP – Glial fibrillary acidic protein

GPCR – G-protein coupled receptor

GRO-α – Growth regulated protein alpha

GVHD – Graft-versus-host-disease

HMOX1 – Heme oxygenase 1

HR – Heart rate

HUVEC – Human umbilical vein endothelial cell

IFN – Interferon

IL – Interleukin

LGS – Lennox-Gastaut syndrome

LPS – Lipopolysaccharide

MC – Medical Cannabis

MCP – Monocyte chemotactic protein

MCT – Monocrotaline

MIP – Macrophage inflammatory protein

MOG – Myelin oligodendrocyte glycoprotein

NRF2 – Nuclear factor-erythroid factor 2-related factor 2

NFκB – Nuclear factor kappa B

OTC – Over-the-counter

PPAR – Peroxisome proliferator-activated receptors

PTSD – Post-traumatic stress disorder

RCT – Randomised controlled trial

ROS – Reactive oxygen species

RVSP – Right ventricular systolic pressure

SBP – Systolic blood pressure

SHR – Spontaneously hypertensive rat

TBI – Traumatic brain injury

THC – Tetrahydrocannabinol

TNF – Tumour necrosis factor

TRP – Transient receptor potential

TRPV1 – Transient receptor potential vanilloid 1

UC – Ulcerative colitis

UGT – Uridine 5'-diphospho-glucuronosyltransferase

USA – United States of America

VCAM-1 – Vascular cell adhesion molecule 1

VEGF-C – Vascular endothelial growth factor C

VEGFR-3 – Vascular endothelial growth factor receptor 3

vGPCR – Viral G protein coupled receptor

WHO – World Health Organization

WR – Wistar rats

CHAPTER 1

INTRODUCTION

1.1 History of cannabis use

Cannabis has been available for centuries and has been the most commonly used illegal substance (Brown and Winterstein, 2019; Burggren et al., 2019). The use of cannabis has a long and notable history, originating in Central Asia, specifically China, before the Christian Era (Zuardi, 2006; Crocq, 2020; Gonçalves et al., 2020; Mlost et al., 2020). Archaeological discoveries suggest that cannabis was utilised by the Chinese to create textiles, thread, paper and rope (Zuardi, 2006; Crocq, 2020). Cannabis fruits were used as food and its seeds were used for treatment of conditions such as constipation, spasms, rheumatic pain, seizures and genitourinary problems (Zuardi, 2006).

In India, medical use of cannabis was extensive, being indicated for pain, epilepsy, inflammation, mental health conditions, spasms, respiratory conditions, lack of appetite and other minor and major ailments (Zuardi, 2006). Its medical use was eventually introduced in the Middle East, Africa and South America between the beginning of the Christian Era and the 16th century (Zuardi, 2006; Crocq, 2020; Gonçalves et al., 2020; Mlost et al., 2020).

The introduction of cannabis for medical use in Europe and North America was reported during the first decades of the 19th century (Zuardi, 2006; Crocq, 2020). In the beginning of the 20th century, in Europe and the United States of America (USA), cannabis was indicated for conditions such as insomnia, mania, bronchitis and allergies, analgesia, chronic inflammation, eczema and dental pain and for other purposes such as lack of appetite, vertigo, diabetes and gastrointestinal problems (Zuardi, 2006; Crocq, 2020). Decades later, the medical use of cannabis in the Western world significantly declined but its recreational use grew significantly in the latter half of the 20th century (Zuardi, 2006). Available dosage forms of recreational cannabis include vape cartridges, oils, raw

plant material, teas, edibles such as sugary sweets and baked goods and topical preparations (Poyatos et al., 2020).

1.2 Cannabis plant and cannabinoids

The cannabis plant has three recognised species, the two main ones being *Cannabis indica* and *Cannabis sativa* (Atakan, 2012). Cannabis consists of hundreds of cannabinoids and effects of these are primarily mediated by cannabinoid (CB) receptors (Sharpe et al., 2020). There are two main types of CB receptors; CB_1 and CB_2 receptors (Atakan, 2012; Baswan et al., 2020; García-Gutiérrez et al., 2020; Kicman and Toczek, 2020; Thibaut and Hoehe, 2020). The centrally located CB_1 receptors are widely distributed throughout the central nervous system (CNS) (Atakan, 2012; Lucas et al., 2018). CB_2 receptors are found in peripheral organs and tissues, predominantly located in the peripheral tissues of the immune system and in the digestive system (Pellati et al., 2018; Baswan et al., 2020). CB receptors form part of the endocannabinoid system, which is involved in mechanisms related to sleep, pain, appetite and the immune system (Atakan, 2012; Brown and Winterstein, 2019). The endocannabinoid system is a complex cell signalling system which comprises of G-protein coupled (GPCR) cannabinoid receptors and their endogenous ligands, endocannabinoids, anandamide (ANA) and 2-arachidonoylglycerol (2AG) (Atakan, 2012; Mlost et al., 2020).

The two most researched cannabinoids are tetrahydrocannabinol (THC) and cannabidiol (CBD) (Atakan, 2012). Both cannabinoids can be found in the cannabis plant however, the content varies according to the species. *Cannabis sativa* has a higher THC content than *Cannabis indica* which consists of a higher CBD content (Atakan, 2012). High levels of CBD together with a low amount of THC, can be found in hemp which is a strain of

Cannabis sativa (Berg et al., 2020). Other cannabinoids include cannabigerol, cannabivarin, cannabinodiol and cannabinol which all produce different pharmacological effects (García-Gutiérrez et al., 2020; Gonçalves et al., 2020).

The effects and pharmacokinetics of cannabinoids may differ depending on the type of cannabinoid, the dosage form and the dose administered (Lucas et al., 2018; Sharpe et al., 2020; Thibaut and Hoehe, 2020). Different concentrations of THC and CBD produce different pharmacological effects (Atakan, 2012; Sharpe et al., 2020). THC is the most psychotropic component of cannabis, producing most of the reported adverse effects experienced with cannabis use (Lucas et al., 2018). THC affects cognition mainly by its agonistic effects on the CB_1 receptors found on the presynaptic axons (Lucas et al., 2018; Gonçalves et al., 2020; Thibaut and Hoehe, 2020). THC was the first psychotropic ingredient of cannabis which demonstrated partial agonist activity on both CB_1 and CB_2 receptors and this led to vast research about the pharmacology, therapeutic potential and adverse effects of THC and eventually to the discovery of the endocannabinoid system (Mlost et al., 2020).

Contrary to THC, CBD is found to have low affinity for CB_1 and CB_2 receptors (Pellati et al., 2018). THC is known to produce psychoactive effects, increase stress and anxiety while CBD, being a non-psychoactive cannabinoid, exhibits antipsychotic effects and generally reduces anxiety, stress and produces a euphoric feeling (Pellati et al., 2018; Afrin et al., 2020).

1.3 Cannabidiol

CBD is one of the most concentrated phytocannabinoids found in the cannabis plant. CBD was first isolated from the cannabis plant in 1940, with its structure, being identified twenty-three years later (Crocq, 2020). CBD and THC have a similar chemical structure though they differ in the spatial configuration which leads to differences in their pharmacological profiles (García-Gutiérrez et al., 2020).

The demand for CBD grew over time with more individuals consuming CBD products for its potential therapeutic uses in humans and animals (Salami et al., 2020). CBD not intended for medicinal use can be found in preparations such as tablets, capsules, oil drops, vape cartridges, topical preparations such as creams, lotions and balms, intranasal sprays and edible CBD gummies (Britch et al., 2020; Brunetti et al., 2020; Link et al., 2020; Wiley et al., 2020). Such preparations may be bought from vape shops, cannabis dispensaries, pharmacies, health shops and online (Haug et al., 2016; Link et al., 2020; Leas et al., 2021).

1.3.1 Pharmacology of cannabidiol

Like other phytocannabinoids, CBD has a high lipid solubility which results in a high distribution in adipose tissues, the brain and other organs (Oberbarnscheidt and Miller, 2020). Due to its extensive first-pass metabolism, CBD has a poor bioavailability especially via the oral route (Britch et al., 2020; García-Gutiérrez et al., 2020; Oberbarnscheidt and Miller, 2020; Wiley et al., 2020). This can be compensated by administering food as it increases the absorption of CBD (García-Gutiérrez et al., 2020; Wiley et al., 2020). A study conducted by Taylor et al., (2018) concluded that when CBD

was administered with high-fat or high-calorie meals the rate and extent of absorption was increased by approximately four to five times (Taylor et al., 2018).

CBD administered through other routes such as transdermal, intravenous or inhalation, may have a better pharmacokinetic profile (Heussler et al., 2019; García-Gutiérrez et al., 2020; Wiley et al., 2020). CBD is considerably metabolised in the liver and is excreted in urine (Britch et al., 2020; García-Gutiérrez et al., 2020).

Besides having an effect on the endocannabinoid system (CB_1 and CB_2 receptors), CBD has over sixty other recognised targets that might potentially produce therapeutic and adverse effects (García-Gutiérrez et al., 2020). These targets include serotonin receptors particularly 1A receptor (5-HT 1A), vanilloid receptors, GPCR, gamma-aminobutyric acid receptors (GABA), glycine and adenosine receptors, fatty acid-binding protein and peroxisome proliferator-activated receptors (PPAR) (Russo, 2017; Brown and Winterstein, 2019; Baswan et al., 2020; Britch et al., 2020; García-Gutiérrez et al., 2020; Kicman and Toczek, 2020). CBD is involved in the metabolism of arachidonic acid via different mechanisms, in the inhibition of various chemicals such as ANA, adenosine, noradrenaline and glutamate and in ion channel effects (Russo, 2017; Brown and Winterstein, 2019; Britch et al., 2020; García-Gutiérrez et al., 2020; Kicman and Toczek, 2020). CBD's diverse and multifaceted mechanism of action might be the explanation for its promising pharmacological purposes (Britch et al., 2020; García-Gutiérrez et al., 2020; Mlost et al., 2020; Kicman and Toczek, 2020).

1.3.2 Potential therapeutic effects

CBD and its potential therapeutic properties have been investigated (García-Gutiérrez et al., 2020). Studies demonstrate that CBD may potentially have anti-tumour properties, analgesic, anti-inflammatory, anti-emetic, anxiolytic, anticonvulsant, cardioprotective, antipsychotic and anti-spasmodic properties (Russo, 2017; Lucas et al., 2018; Huestis et al., 2019; Kis et al., 2019; Britch et al., 2020; García-Gutiérrez et al., 2020; Kicman and Toczek, 2020; Mlost et al., 2020). The anticonvulsant activity of CBD led to the approval of CBD for the treatment of drug-resistant epilepsy (Britch et al., 2020; Brunetti et al., 2020; Kicman and Toczek, 2020). Further research is being conducted on other therapeutic effects of CBD (Jones and Vlachou, 2020; Rapin et al., 2021).

1.3.3 Adverse effects and toxicity

There are adverse effects related to CBD use (Chesney et al., 2020; Wiley et al., 2020). Common adverse reactions experienced in humans include gastrointestinal problems such as diarrhoea, vomiting and nausea, changes in behaviour, drowsiness, pneumonia, sedation, fatigue and hepatobiliary disorders such as elevations in aspartate aminotransferase (AST) and alanine transaminase (ALT) (Devinsky et al., 2018; Huestis et al., 2019; Chesney et al., 2020; Wiley et al., 2020). In a study conducted by Moltke et al., (2021), 71% of respondents taking CBD did not experience any adverse effects (Moltke et al., 2021). In a cross-sectional study carried out by Corroon and Phillips (2018), dry mouth, euphoria, increase in appetite, red eyes and somnolence were adverse effects commonly reported by participants (Corroon and Phillips, 2018).

In animals, side effects related to CBD consisted of hypotension, inhibition of CNS activity, neurotoxicity, hepatotoxicity and organ weight changes (Huestis et al., 2019).

Huestis et al., (2019) suggested that the adverse effects experienced in animals may have been due to the high CBD concentrations used (Huestis et al., 2019).

CBD is metabolised by the liver via the cytochrome P450 system and the uridine 5'-diphospho-glucuronosyltransferase (UGT) enzymes (Lucas et al., 2018; Huestis et al., 2019; Chesney et al., 2020). Other concomitant drugs that are also metabolised by the liver, such as antiepileptic drugs, may give rise to drug-to-drug interactions (Morrison et al., 2019; Wiley et al., 2020). It has been reported that CBD interacts with clobazam, stiripentol and valproate (Huestis et al., 2019; Morrison et al., 2019). The mechanism of the interaction between CBD and valproate is yet to be known (Chesney et al., 2020).

1.4 Legal status of cannabis and cannabidiol

In the European Union (EU), any CBD-based medicinal product placed on the market of a Member State requires a community marketing authorisation, issued by the European Agency for Evaluation of the European Medicines Agency (Brunetti et al., 2020). In January 2019, all extracts of *C. sativa* L., including CBD were classified under the EU Novel Food Regulation (Brunetti et al., 2020; McGregor et al., 2020). Cannabinoids cannot be placed on the market in the EU without undergoing safety assessment under the Novel Food Regulation (Brunetti et al., 2020). Cosmetics which contain CBD may be placed on the EU market if they are in accordance with the Cosmetic Regulation (Brunetti et al., 2020). In November 2020, the European Court of Justice concluded that CBD extracted from the cannabis plant is not considered a narcotic drug[1].

[1] European Monitoring Centre for Drugs and Drug Addiction. Cannabidiol (CBD) is not considered a "narcotic drug" under European law | www.emcdda.europa.eu [Internet]. www.emcdda.europa.eu. 2020 [cited 2021 Nov 1]. Available from: https://www.emcdda.europa.eu/news/2020/cannabidiol-cbd-is-not-considered-a-narcotic-drug-under-european-law_en

The World Health Organization's (WHO) expert committee on Drug Dependence found that CBD does not produce potential dependence and abuse. Regarding the issue of CBD purity, during the 63rd session, the WHO proposed to the United Nations Commission on Narcotic Drugs to add the following footnote on the list of narcotic drugs:

"Preparations containing predominantly cannabidiol and not more than 0.2 per cent of delta-9-tetrahydrocannabinol are not under international control".

This footnote was rejected (2020)[2]. According to Annex II of Regulation (EC) No 1223/2009, the use of CBD derived from tincture or extract or resin of cannabis in cosmetics is prohibited to be used. Synthetically produced CBD or natural CBD derived from cannabis tincture, cannabis extract or cannabis resin originating from leaves and seeds that are not accompanied with the flowering tops of the cannabis plant, can be used in cosmetics. In Europe, cosmetics should not contain more than 0.2 per cent of THC (McGregor et al., 2020; Ukaegbu et al., 2021). In Malta, CBD is available as oil drops, tablets and flowers. CBD is not considered a narcotic drug, instead it is qualified as a novel food (Brunetti et al., 2020). CBD preparations containing less than 0.2 per cent of THC are not under international control (McGregor et al., 2020).

In all European countries except Malta, cannabis for personal use is illegal. As from 18th December 2021, Malta became the first EU Member state to legalise the restricted cultivation of cannabis and the restricted recreational use of cannabis[3]. In Malta, Medical Cannabis (MC) is also available and approved as raw plant material. Currently there are

[2]United Nations. Current scheduling recommendations [Internet]. United Nations: Office on Drugs and Crime. 2020 [cited 2021 Jun 15]. Available from: https://www.unodc.org/unodc/en/commissions/CND/Mandate_Functions/current-scheduling-recommendations.html

[3] DRUG DEPENDENCE (TREATMENT NOT IMPRISONMENT) ACT (Cap. 537) [Internet]. 2015 [cited 2022 Jan 03]. Available from: https://legislation.mt/eli/cap/537/eng/pdf

eight cannabinoid containing medicinal products available in Malta which can be found in Table 1.1.

Table 1.1 Medical Cannabis products available in Malta

Medicinal product name	**THC: CBD composition**	**Dosage form**	**Pack content in grams (g)**
Aphria® 22/1	22% THC: <1% CBD	Dried cannabis flowers	5g
Bediol®	6.3% THC: 8% CBD		5g
Bedrocan® 22/1	22% THC: <1% CBD		5g
Cannabis 1A 18/1	18% THC: <1% CBD		10g
CARBASI®	21.7% THC: ≤1% CBD		15g
Pedanios® 20/1	20% THC: <1% CBD		10g
Pedanios® 22/1	22% THC: <1% CBD		10g
ZeraUltra®	22% THC: <1% CBD		10g

In the USA, there are 36 states that allow MC and 18 states that legalised cannabis for recreational use (McGregor et al., 2020). However, cannabis is still classified under Schedule I of the Controlled Substances Act meaning that it has no current accepted medical use and has a high potential for abuse (Berg et al., 2020; Brunetti et al., 2020). In 2018, the Food and Drug Administration (FDA) approved Epidiolex®. Epidiolex® containing purified 100mg CBD per ml, is the only FDA approved CBD-based product used for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS) in conjunction with clobazam, in patients aged 2 years and above and is also indicated as adjunctive therapy of seizures associated with tuberous sclerosis

complex for patients aged 2 years and above (Corroon and Phillips, 2018; Brunetti et al., 2020). This CBD-based product is also approved by the European Medicines Agency (EMA) and is authorised in different EU countries under the European name Epidyolex®. Following market approval, Epidiolex® was classified under Schedule V which is the least restrictive schedule of the Controlled Substance Act. Drugs classified under Schedule V are considered to have a lower risk for abuse than Schedule VI (Brunetti et al., 2020).

In 2018, hemp together with any cannabinoids including CBD or derivatives which can be obtained from hemp were no longer controlled substances under US federal law, so long as that they contain no more than 0.3 percent THC on a dry weight basis[4]. Although products containing CBD derived from hemp are legal, they are not approved by the FDA and cannot be distributed or sold from one state to the other (Brown and Winterstein, 2019; Brunetti et al., 2020). Cosmetics containing CBD are not limited by any laws but they cannot be used if the ingredients cause debasement or can cause injuries to the users or if there is mislabelling of the product (Brunetti et al., 2020).

1.5 Myths and misconceptions

CBD is shown to have therapeutic effects without causing significant adverse effects (Crippa et al., 2020). Merrick et al., (2016) suggested that in humans CBD converts to THC and this can lead to psychotic side effects (Merrick et al., 2016). Crippa et al., (2020) concluded that after oral administration of CBD, THC was not detected in plasma and CBD exhibited no psychotic effects (Crippa et al., 2020). It is thought that when THC

[4] Members of Congress. AGRICULTURE IMPROVEMENT ACT OF 2018 [Internet].2018 [cited 2021 Jun 15]. Available from: https://www.congress.gov/115/plaws/publ334/PLAW-115publ334.pdf

and CBD are used in combination, there is a potential decrease in the adverse effects of THC due to CBD (Pellati et al., 2018). Such adverse effects of THC include anxiety, nausea, paranoia, confusion, short-term memory loss and tachycardia (Pellati et al., 2018). Conversely, CBD products contaminated by THC might be the reason for adverse psychoactive effects as CBD extraction with contamination of THC is possible (Britch et al., 2020; Lachenmeier et al., 2020). THC doses of 10mg to 20mg in smoked cannabis can produce toxic effects such as tachycardia, anxiety, sedation and agitation. (Lachenmeier et al., 2020). One of the CBD oil supplements analysed in the Lachenmeier et al., (2020) study, contained 30mg of THC which explains the dysphoria and 'high' side effects experienced by users (Lachenmeier et al., 2020). A study by Bonn-Miller et al., (2017) showed that out of the 84 CBD products analysed, only 26 were accurately labelled and different concentrations of THC were detected in 18 CBD products (Bonn-Miller et al., 2017). The THC concentration ranged from 0.00 mg/mL to 6.43 mg/mL (Bonn-Miller et al., 2017). A 2021 study by Mazzetti et al. found that CBD concentrations in e-liquids were lower than the stated concentrations (Mazzetti et al., 2021).

CBD is frequently reported to not have any psychoactive or psychotropic effects unlike THC (Pellati et al., 2018; Afrin et al., 2020). Russo (2017), views this as an inaccurate claim, since CBD has been reported to produce pharmacological benefits on mental health disorders such as schizophrenia, depression, anxiety and addiction (Russo, 2017; Kicman and Toczek, 2020). Russo (2017) and Kicman and Toczek (2020), suggest that CBD should be described as non-intoxicating, rather than non-psychoactive or non-psychotropic (Russo, 2017; Kicman and Toczek, 2020). Another misconception is that CBD might produce dependence or withdrawal symptoms upon stopping use (Leszko and Meenrajan, 2021).

There are contradictory data about the sedating or non-sedating effects of CBD (Russo, 2017). A study by García-Gutiérrez et al., (2020) reported that CBD does not have sedating properties and Russo (2017) explained that products containing CBD may be sedating but pure CBD does not produce sedation (Russo, 2017; García-Gutiérrez et al., 2020). In the study conducted by Huestis et al., (2019) sedation was reported to be one of the most frequent side effects experienced by participants. Sedation and somnolence are listed as very common adverse effects which can occur with use of Epidyolex®/ Epidiolex® which consists of 100mg pure CBD (Huestis et al., 2019).

Leszko and Meenrajan (2021) demonstrated the need for awareness about the difference between CBD and MC as the general public often confuse CBD with MC (Leszko and Meenrajan, 2021). In a study by Schilling et al., (2021), the majority of participants knew the difference between MC and CBD (Schilling et al., 2021).

1.6 Attitudes and perceptions

At present, Epidiolex®/Epidyolex® is the only product containing solely CBD with an approved therapeutic effect (Brunetti et al., 2020; Leas et al., 2020). Since no other CBD product is approved to treat and manage medical conditions, the FDA forbids health claims or the promoting of medical benefits related to the use of unapproved CBD products (Berg et al.,2020; Corroon et al., 2020; Leas et al., 2020). CBD products have been advertised as dietary supplements and as natural remedies for medical conditions (Rapin et al., 2021). Consumers have reported CBD products to be useful and effective in treating conditions such as chronic pain, arthritis and mental health disorders (Corroon and Phillips, 2018; Leas et al., 2020; Fortin et al., 2021; McFadden and Malone, 2021).

In a study conducted by Corroon and Phillips (2018), 76% of the respondents stated that they learnt about CBD from family members, friends or the internet (Corroon and Phillips, 2018). Thirty-five percent of the respondents stated that CBD was very effective when used alone (Corroon and Phillips, 2018). A study by Berg et al., (2020) demonstrated that managers or owners of vape shops feel comfortable selling CBD as it lacks psychoactive effects and its potential therapeutic uses outweigh the minimal risks (Berg et al., 2020). It demonstrated that customers found CBD helpful in the management of pain and sleep disorders, among other conditions (Berg et al., 2020). Participants from a study by Lovecchio et al., (2021) study, found CBD to be effective in spine-related pain (46%) and spine-related complaints such as sleep problems (33%) and anxiety (20%) (Lovecchio et al., 2021). Twenty-four percent of the participants reported that CBD had no therapeutic effects (Lovecchio et al., 2021).

According to Link et al., (2020), pharmacists working in the USA lacked knowledge about over-the-counter (OTC) CBD products and they felt incompetent or unprepared in giving advice to patients about CBD and discussing the use of OTC CBD products with other healthcare professionals (Link et al., 2020). Two major concerns that pharmacists reported were the level of safety of OTC CBD products and its quality consistency (Link et al., 2020). Patient concerns reported by Wershoven et al., (2020) included limited scientific data to help guide healthcare professionals, adverse effects of cannabinoids, potential for abuse and potential effects on driving (Wershoven et al., 2020). Leszko and Meenrajan (2021) showed that a common concern of patients was that they might be judged or misunderstood by physicians if they knew that CBD was being used by them (Leszko and Meenrajan, 2021). Caregivers suggested that CBD should not be available over the counter but should be regulated by the government and labelled as a medicine (Leszko and Meenrajan, 2021). The concern of being judged or misunderstood for using

CBD or cannabis was another barrier expressed by autistic and non-autistic participants (Hua et al., 2021).

Healthcare professionals and non-healthcare professionals working in cannabis dispensaries expressed that they would likely recommend high CBD products in epilepsy, arthritis, muscle spasms, Alzheimer's disease (AD) and amyotrophic lateral sclerosis (ALS) (Haug et al., 2016). In a study carried out by McFadden and Malone (2021), CBD was perceived as a drug with a therapeutic purpose whilst having a low risk for abuse (McFadden and Malone, 2021). In a study by Schilling et al., (2021) participants disagreed that CBD is harmful (75%) or addicting (65%) (Schilling et al., 2021).

1.7 Aims and objectives

The aim of the study was to investigate the science, myths and realities related to CBD.

The objectives of the study were to:

i. Compare research related to potential therapeutic benefits of CBD
ii. Assess the knowledge and perception of the general public about CBD
iii. Assess the knowledge and perception of healthcare professionals about CBD

CHAPTER 2

METHODOLOGY

The methodology includes a systematic literature search about available studies demonstrating the potential therapeutic benefits of CBD in different medical conditions and the development of two questionnaires which aim to assess the perception of the public and healthcare professionals about CBD.

2.1 Systematic literature search

A systematic search was carried out in February 2021 using PubMed as the main search engine. The focus of the literature review was on open access peer reviewed journal articles published in English. The filters applied were the following: 'Free full text'; 'Full text'; 'English' and 'studies from 01/2010 – 12/2020'. Table 2.1 shows the inclusion and exclusion criteria of the literature review.

The keywords used for the search were the following: (cannabidiol AND medical conditions); (therapeutic effects (cannabidiol OR CBD)); (approved indications of cannabidiol); (cannabidiol AND (medicinal OR therapeutic use)); (cannabidiol AND indications); (cannabidiol AND medical disorders); (benefits of cannabidiol) and (potential effect of cannabidiol).

The PRIMSA style method was employed (Moher et al., 2009). The studies included in the qualitative synthesis were analysed and comparisons were made. The impact factor of the journals containing the studies was identified.

Table 2.1 Inclusion and exclusion criteria of systematic literature search

Category	**Inclusion Criteria**	**Exclusion Criteria**
Year of publication	2010-2020	Anything published before 2010 and after December 2020
Type of publication	● Open access ● Full text available ● Peer reviewed ● Experimental studies e.g., randomised and non-randomised controlled trials ● Observational studies e.g., cohort studies, case studies	● Closed access ● Full text not available ● Non - peer reviewed ● Publications that are not experimental studies nor observational studies ● Ongoing studies or no results provided
Language	English	Language other than English
Main topic of research	● Approved or potential therapeutic effects of CBD in different medical conditions ● CBD used alone ● Purified, high CBD extract, CBD hemp-based oil included	● CBD use for non-medical conditions ● CBD derivatives, synthetic CBD, abnormal CBD ● CBD in combination with THC or any other drug ● CBD compared with other drugs
Region of research	Global	N/A

2.2 Questionnaires

Two questionnaires aiming to assess the perception of the general public and health care professionals were developed (Appendix 1). The questionnaire for general public was available in English and Maltese. An information sheet for the participants which briefly explained the aims of the study and what their participation entails of was designed in English and Maltese (Appendix 2). The questionnaires were developed electronically using Google Forms©.

2.2.1 Questionnaire design

Both questionnaires consisted of four sections: Section A, B, C and D. Appendix 1 details the full questionnaires and Table 2.2 explains how each section of the questionnaire fulfils part of the aim and two objectives of the study.

Table 2.2 Information about each section of the questionnaires

Section and information included	**Questionnaire for General Public**	**Questionnaire for Healthcare Professionals**
Section A	Section A aimed to collect the participant's demographics in order to analyse any significant trends of knowledge or perception about CBD within demographic groups.	
Section B	Section B focused on determining the extent of public knowledge about CBD. This section provided a deeper insight into public knowledge about CBD and helped determine any misconceptions believed by the general public. The public knowledge about the therapeutic effects and side effects of CBD was further assessed. The side effects listed in Question 6 were all common or very common side effects caused by Epidiolex® / Epidyolex®.	Section B aimed to assess whether healthcare professionals were more knowledgeable about CBD than non-healthcare professionals. It focused on various subjects related to CBD ranging from pharmacology, legal status, safety profile, therapeutic effects and side effects of CBD. The side effects listed in Question 5 were all common or very common side effects caused by Epidiolex® / Epidyolex®.
Section C	Section C focused on collecting the perception and opinion of the general public about CBD, its legality and intended use.	Section C focused on understanding the perception of healthcare professionals about the legality of CBD products in Malta. It provided a deeper insight about whether healthcare professionals would feel comfortable in prescribing or recommending CBD and it further investigated healthcare professionals' perceptions and opinions about CBD.
Section D	Section D targeted potential barriers that might be related to CBD use.	

2.2.2 Validation

Validation of the questionnaires was carried out through discussion with a panel of seven experts which consisted of:

- Three pharmacists; one industrial, one community and one responsible pharmacist of a medical cannabis production pharmaceutical company
- One general practitioner
- One physiotherapist
- Two lay persons; a shop manager and a pensioner.

Each expert was handed the questionnaires and information letter in both English and Maltese, in person or via email. A validation sheet (Appendix 3) was given to each expert to help them validate both questionnaires. The validation sheet was the same for both questionnaires. It included seven statements with a Likert Scale where the experts had to tick a given statement according to their level agreement, from strongly disagree to strongly agree. The validation sheet al.so included one open-ended question, which asked the experts for any further suggestions for improvement. The validation sheet was also developed electronically using Google Forms©.

The two lay persons were not asked to validate the questionnaire intended for healthcare professionals. The questionnaire intended for the healthcare professionals was validated by five healthcare professionals, while the questionnaire intended for the general public was validated by all seven experts.

For the questionnaire aimed at the general public, all seven experts of the validation panel agreed with the seven statements provided and no major adjustments were demanded. Three out of seven experts suggested using simpler terms or including the meaning in brackets, for the terminology used in question 5 of Section B. The following changes were carried out:

- The inclusion of ‘manages psychosis’ in brackets next to ‘Antipsychotic’; ‘prevents or inhibits the formation or growth of tumours’ in brackets next to ‘Antitumour’; ‘treats epilepsy’ in brackets next to ‘Antiepileptic’; ‘prevents or slows damage to cells’ in brackets next to ‘Antioxidant’; ‘treats depression’ in brackets next to ‘Antidepressant’; ‘improves conditions related to the heart and blood vessels’ in brackets next to ‘Cardiovascular’; ‘protects nerve cells from damage, impairment’ in brackets next to ‘Neuroprotective’ and ‘reduces anxiety’ in brackets next to ‘Anxiolytic’
- The change of the word ‘Analgesic’ to ‘Pain killer’
- Rewording ‘CBD has a lower risk of psychoactive effects compared to THC’ to ‘CBD has a lower risk of producing mental effects compared to THC’, in question 3 of Section B.

For the questionnaire intended for healthcare professionals, the five experts of the validation panel agreed with the seven statements provided and no major adjustments were demanded however, the following suggestions were recommended and implemented:

- The separation of 'EMA and FDA approved indications of CBD' in question 3 of Section B into 'EMA approved indication of CBD' and 'FDA approved indications of CBD'
- The inclusion of 'Not sure' in question 6 of Section B
- Clarifying that those participants who answer 'Yes' or 'Not sure' in question 6 of Section B, are required to answer the next questions before moving onto Section C.

Once the changes were applied to the questionnaires, all the experts were consulted again and they all agreed that the questionnaires are a suitable research tool.

2.2.3 Ethics Approval

Research Ethics approval (Appendix 4) was sought and granted by the Faculty Research Ethics Committee (FREC), Faculty of Medicine and Surgery, in June 2021, prior to dissemination of the questionnaires.

2.2.4 Dissemination and data collection

Recruitment of participants was carried out by means of convenience sampling. The electronic questionnaires were uploaded through social media via Facebook and

LinkedIn. The questionnaire intended for healthcare professionals was additionally disseminated through all the available professional associations such as Malta Chamber of Pharmacists, Medical Association of Malta, Allied Health Services, Malta College of Family Doctors and so forth. The questionnaire for the general public consisted of two URL links representing both Maltese and English options and eliminating any language barriers.

Besides distributing the questionnaires electronically, patients and healthcare professionals attending pharmacies were asked if they would like to participate voluntarily. Prior to participating in the questionnaire, a detailed verbal explanation of what the research consists of, together with the information sheet (Appendix 2) were provided to the participants. When data collection was executed in person, a box with a slit was used so that upon completion of the questionnaire, the participants could place it in the box and remain anonymous. The questionnaires in paper format were then inputted in Google Forms© so as to view the responses in real time.

2.2.5 Data analysis

For each questionnaire, the responses, both electronically and in paper format, were inputted in a spreadsheet using Microsoft® Excel 2019. IBM SPSS software version 28 was used to analyse the data collected. The Friedman test, Kruskal Wallis test and Chi-square test were the statistical tests used to analyse the data collected.

The Friedman test was used to compare mean rating scores between a number of related statements. These mean rating scores range from 1 to 5, where 1 corresponds to strongly disagree and 5 corresponds to strongly agree.

The error bar graph displays the 95% confidence interval for the actual mean rating score provided to the statement if the whole Maltese population had to participate in this study. When two confidence intervals overlap considerably, this indicates that their mean rating scores are similar and do not differ significantly. Conversely, when two confidence intervals are disjointed or overlap slightly, this indicates that their mean rating scores differ considerably.

The Kruskal Wallis test was used to compare mean rating scores provided to a statement between groups of participants clustered by demographic variables such as gender, age, level of education and nationality and by other categorical variables. These mean rating scores range from 1 to 5, where 1 corresponds to strongly disagree and 5 corresponds to strongly agree.

The Chi-square test was used to investigate the association between two categorical variables.

Following data analysis, 3 abstracts were submitted for the 80th International Pharmaceutical Federation (FIP) World Congress of Pharmacy and Pharmaceutical Sciences being held in Seville, Spain, in September 2022. All three abstracts were accepted for poster presentations (Appendix 13).

CHAPTER 3

RESULTS

3.1 Systematic literature search results

A total of 2,637 articles were identified, of which 126 articles met the inclusion criteria for review. Flow of information is presented in the PRISMA flow chart (Figure 3.1)

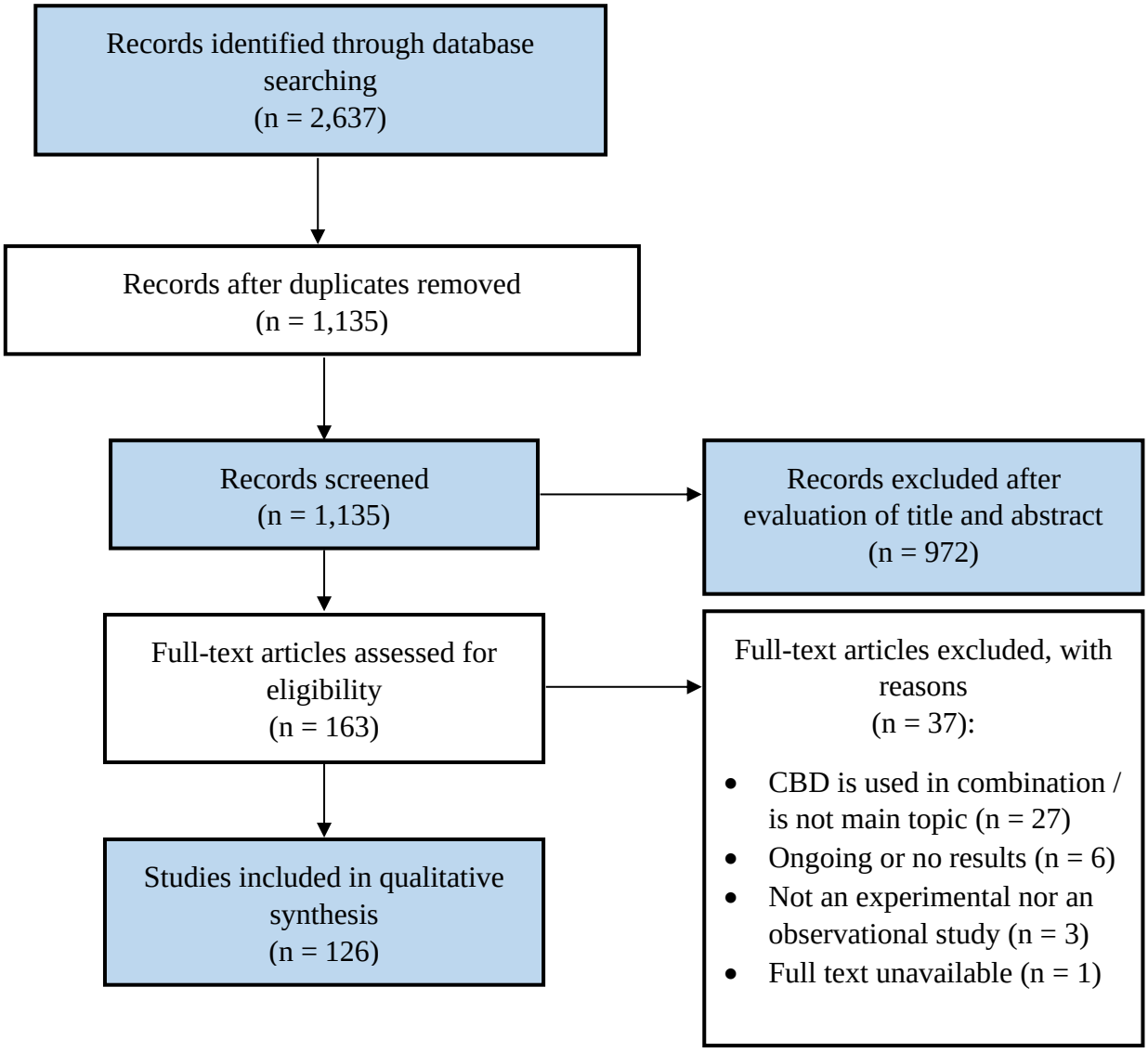

Figure 3.1 PRISMA style flow chart of systematic search of literature review

Adapted from Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Medicine. 2009;6(7): e1000097.

Out of 126 studies, 33 demonstrated that CBD had an effect on mental health disorders, 27 reported anti-inflammatory and anti-oxidant effects, 21 reported an effect on neurological disorders, 15 demonstrated anti-tumour, apoptotic and antiangiogenic effects, 11 showed cardioprotective effects, 6 studies showed that CBD had an effect on different types of pain, 5 revealed neuroprotective effects and 8 studies exhibited that CBD had other therapeutic effects. Fifty-five of the 126 studies were animal studies, 33 were human studies, 23 were *'in vitro'* and 15 were both *'in vitro'* and animal studies.

3.1.1 Effects on mental health disorders

Thirty-three studies investigated the potential effects of CBD on mental health disorders (Hallak et al., 2010; Bergamaschi et al., 2011; Scopinho et al., 2011; Uribe - Mariño et al., 2011; Barichello et al., 2012; Almeida et al., 2013; Campos et al., 2013; Seeman, 2016; Shannon and Oplia-Lehman, 2016; Libro et al., 2017; Osborne et al., 2017; Bhattacharyya et al., 2018; Gonzalez-Cuevas et al., 2018; Hindocha et al., 2018; Linares et al., 2018; Navarette et al., 2018; Peres et al., 2018; Belardo et al., 2019; Bolsoni et al., 2019; Hermush and Ore, 2019; Heussler et al., 2019; Linares et al., 2019; Shannon et al., 2019; Pretzsch et al., 2019a,b; Wilson et al., 2019; Appiah-Kusi et al., 2020; Bloomfield et al., 2020; Coles et al., 2020; Davies et al., 2020; Gáll et al., 2020; Lawn et al., 2020; Patra et al., 2020). Characteristics of these studies are summarised in Appendix 5.

The 33 studies consisted of 12 animal studies, 11 randomised controlled trials (RCTs), 4 case reports, 3 clinical trials and 3 '*in vitro'* studies.

CBD reported to have an effect in anxiety and related disorders (16), psychosis (6), cognitive deficit disorders (6), schizophrenia (2), autism (2) and eating disorders (1).

The impact factor of the 33 studies ranged between 1.036 (The Israel Medical Association Journal) and 21.6 (Journal of the American Medical Association of Psychiatry) with an average impact factor of 5.31.

Anxiety and related disorders

The 16 publications consisted of 7 animal studies, 3 RCTs, 3 case reports, 2 clinical trials and 1 '*in vitro'*.

The 7 animal studies and 1 *'in vitro'* studies demonstrated that CBD produced an anti-aversive effect, prevented an anxiogenic effect, decreased anxiety and depressive-like behaviours and improved social behaviour and memory function (Uribe- Mariño et al., 2011; Almeida et al., 2013; Campos et al., 2013; Gonzalez-Cuevas et al., 2018; Navarette et al., 2018; Gáll et al., 2020; Patra et al., 2020). CBD had no effect on anxiety levels nor on the overall effect on sensorimotor gating. CBD did not have a significant effect on motor function (Coles et al., 2020).

The 8 human studies displayed that CBD greatly decreased anxiety and cognitive impairment, improved sleep and eased mood and depression (Bergamaschi et al., 2011; Shannon and Oplia-Lehman, 2016; Bolsoni et al., 2019; Heussler et al., 2019; Linares et al., 2019; Shannon et al., 2019). Conversely, CBD had no significant effect on the polysomnography, reward anticipation and feedback nor on behavioural measures of motivation for reward (Linares et al., 2018; Lawn et al., 2020).

Psychosis

The 6 studies consisted of 4 RCTs, 1 *'in vitro'* and 1 animal study.

The 4 RCTs demonstrated that participants at clinical high risk (CHR) of psychosis who received CBD had a lower activation in a cluster in the left parahippocampal gyrus or in the left insula/parietal operculum and an intermediate activation in the parahippocampal gyrus (Bhattacharyya et al., 2018; Wilson et al., 2019; Davies et al., 2020). Participants with CHR for psychosis who received CBD had an intermediate level of anxiety (Appiah-Kusi et al., 2020).

The *'in vitro'* study showed that CBD inhibited the binding of domperidone at the brain dopamine 2 receptors indicating potential antipsychotic effects (Seeman, 2016).

The animal study demonstrated that CBD reduced attacks of aggressive behaviour in mice with traumatic brain injury (TBI) and improved sociability. Chronic CBD treatment reduced behavioural dysfunctions (Belardo et al., 2019).

Cognitive deficit disorders

The 6 studies consisted of 2 animal studies, 2 RCTs, 1 case and 1 *'in vitro'*. The 2 animal studies demonstrated that CBD prevented memory impairment in rats with pneumococcal meningitis and CBD improved recognition, working memory and social interaction (Barichello et al., 2012; Osborne et al., 2017).

One RCT showed that CBD did not improve spatial nor verbal working memory and it had no effect on the impulsivity experienced during tobacco abstinence. CBD was ineffective in reversing the cognitive impairments related with acute nicotine abstinence (Hindocha et al., 2018). The other RCT revealed that CBD increased cerebral blood flow

in the hippocampus. No differences in memory task performance were exhibited (Bloomfield et al., 2020). The case report concluded that CBD increased alertness and responsiveness and attenuated spasticity in a patient with dementia (Hermush and Ore, 2019).

In the *'in vitro'* study, CBD downregulated expression of the genes linked to AD. CBD upregulated genes related to catabolic protein processes and inhibited glycogen synthase kinase 3 beta, an important player in Alzheimer's disease (AD) pathogenesis (Libro et al., 2017).

Schizophrenia

In the clinical trial carried out by Hallak et al., (2010), CBD administered to 28 schizophrenic patients before being subjected to a word test, improved performance and decreased the number of errors experienced (Hallak et al., 2010).

The animal study demonstrated that CBD prevented the development of increased locomotor activity. CBD increased social interaction in wistar rats (WRs). CBD increased levels of serotonin. CBD did not induce catalepsy nor tardive dyskinesia (Peres et al., 2018).

Autism

Both studies were RCTs. CBD treatment in participants with autism altered vermal functional connectivity and increased fractional amplitude of low-frequency fluctuations in the cerebellar vermin and the right fusiform gyrus (Pretzsch et al., 2019a). CBD affected both glutamate and GABA levels in adults with or without autism (Pretzsch et al., 2019b).

Eating disorders

CBD reduced hyperphagia in both fasted and fed rats (Scopinho et al., 2011

3.1.2 Anti-inflammatory and anti-oxidant effects

Anti-inflammatory and anti-oxidant effects produced by CBD were exhibited in 27 studies (Liu et al., 2010; De Filippis et al., 2011; Kozela et al., 2011; Ruiz-Valdepenas et al., 2011; Karmaus et al., 2012; Ribeiro et al., 2012; Schicho and Storr, 2012; Mecha et al., 2013; Yang et al., 2014; Giacoppo et al., 2015a; Hammell et al., 2015; Kozela et al., 2015; Singer et al., 2015; Vuolo et al., 2015; Libro et al., 2016; Kozela et al., 2016; Philpott et al., 2017; Wang et al., 2017; Callejas et al., 2018; Elliott et al., 2018; Li et al., 2018; Gegotek et al., 2019; Jastrząb et al., 2019; Muthumalage and Rahman, 2019; Casares et al., 2020; Jarocka-Karpowicz et al., 2020; Atalay et al., 2020). The study characteristics are summarised in Appendix 6.

Sixteen studies were animal studies where 12 used mice and 4 used rats. Eight studies were *'in vitro'* and three studies were both *'in vitro'* and animal studies where the subjects used were mice.

The 16 animal studies demonstrated that CBD:

- Decreased the expression of pro-inflammatory cytokines such as tumour necrosis factor (TNF) – alpha, Interferon (IFN) -gamma and interleukins (IL) particularly IL-4, IL-5, IL-13, IL-6 (Liu et al., 2010; Ruiz-Valdepenas et al., 2011; Ribeiro et al., 2012; Giacoppo et al., 2015a; Hammell et al., 2015; Vuolo et al., 2015; Wang et al., 2017; Li et al., 2018).

- Reduced microglial stimulation, leukocytes, T-cell recruitment, myelin oligodendrocyte glycoprotein (MOG)-induced inflammation and cyclooxygenase-2 (COX-2) levels (Kozela et al., 2011; Ruiz-Valdepenas et al., 2011; Philpott et al., 2017).
- Decreased monocyte chemotactic protein (MCP)-1, macrophage inflammatory protein (MIP)-2 concentrations and myeloperoxidase activity (Ribeiro et al., 2012; Schicho and Storr, 2012; Wang et al., 2017).
- Decreased oxidative/nitrative stress (Yang et al., 2014; Wang et al., 2017; Callejas et al., 2018).
- Increased IL-10 which is an anti-inflammatory cytokine (Giacoppo et al., 2015a; Vuolo et al., 2015).
- Modulated the production of Treg cells, CD4 and CD8α T-cells and reduced glial fibrillary acidic protein (GFAP) expression (Giacoppo et al., 2015a).
- Increased a central antioxidant enzyme (Atalay et al., 2020).

Conversely, Karmaus et al., (2012) demonstrated that CBD increased the levels of monocytes and inflammatory cells in lipopolysaccharide (LPS) induced pulmonary inflammation. Singer et al., (2015) demonstrated that CBD increased ROS levels.

The 8 *'in vitro'* studies reported that CBD suppressed genes linked to apoptosis, inflammation and innate immune responses (Libro et al., 2016). CBD reduced increased levels of TNF-alpha levels, upregulated T lymphocytes and increased early growth response (EGR2) mRNA transcription and increased anergy promoting genes such as IL-10 (De Filippis et al., 2011; Kozela et al., 2015; Kozela et al., 2016). CBD decreased ROS levels UV-irradiated keratinocytes of healthy participants yet in the keratinocytes of

psoriatic participants following UV irradiation CBD increased the oxidative and inflammatory state (Jarocka-Karpowicz et al., 2020). CBD showed differential pro- and anti-inflammatory effects by ROS levels. CBD significantly attenuated LPS-induced nuclear factor kappa B (NF-κB) activity and IL-8 and MCP-1 (Muthumalage and Rahman, 2019).

The anti-oxidant effect was produced via:

- Changes in protein expressions related to antioxidant effects and inflammation (Gegotek et al., 2019).
- Increasing the effects of antioxidant enzymes such as superoxide dismutase and thioredoxin reductase (Jastrząb et al., 2019).

The 3 '*in vitro'* and animal studies showed that CBD has anti-inflammatory and long-term immunomodulatory effects (Mecha et al., 2013). CBD reduced levels of IFN-gamma and IL-17, attenuated pro-inflammatory cytokines (IL-10), upregulated heme oxygenase 1 (HMOX1) and activated the transcriptional activity of nuclear factor-erythroid factor 2-related factor 2 (NRF2) (Elliott et al., 2018; Casares et al., 2020).

The impact factor of the 27 studies ranged between 2.59 (Brazilian Journal of Medical and Biological Research) and 11.799 (Redox Biology) with an average of 5.55.

3.1.3 Effects on neurological conditions

CBD's effect on neurological conditions was demonstrated by 21 studies (Avraham et al., 2011; Jones et al., 2012; Gomes et al., 2013; Hess et al., 2016; Peres et al., 2016; Devinsky et al., 2017; Do Val-da Silva et al., 2017; Kaplan et al., 2017; Álvarez Bravo et al., 2018; Devinsky et al., 2018a,b,c; Khan et al., 2018; Maggio et al., 2018; Szaflarski et al., 2018;

Gu et al., 2019; Thiele et al., 2019; Anderson et al., 2020; Gray et al., 2020; Koo et al., 2020; D'Onofrio et al., 2020). Characteristics of these studies are summarised in Appendix 7.

Nine studies were animal studies out of which 6 used mice and 3 used rats as the subject. Seven were clinical trials, 3 were RCTs, 1 was a case report and 1 was an '*in vitro'* and animal study.

The 9 animal studies and 1 *'in vitro'* and animal studies demonstrated that CBD improved neurological score, behaviour and cognitive function, decreased seizure frequency, severity and activity, decreased cataleptic effects, protected mice against seizures and increased seizure threshold (Avraham et al., 2011; Jones et al., 2012; Gomes et al., 2013; Peres et al., 2016; Do Val-da Silva et al., 2017; Kaplan et al., 2017; Khan et al., 2018; Maggio et al., 2018; Gu et al., 2019; Gray et al., 2020).

The 11 human studies showed that CBD reduced the frequency and severity of seizures and improved cognitive and motor abilities and behaviour (Hess et al., 2016; Devinsky et al., 2017; Álvarez Bravo et al., 2018; Devinsky et al., 2018a, b, c; Szaflarski et al., 2018; Thiele et al., 2019; Anderson et al., 2020; D'Onofrio et al., 2020; Koo et al., 2020).

The impact factor of the 21 studies ranged between 2.153 (Journal of Korean Medical Science) and 91.245 (The New England Journal of Medicine) with an average impact factor of 14.39.

3.1.4 Anti-tumour, antiangiogenic and apoptotic effects

CBD demonstrated anti-tumour, antiangiogenic and apoptotic effects in 15 studies (McAllister et al., 2011; Shrivastava et al., 2011; Maor et al., 2012; Solinas et al., 2012; Solinas et al., 2013; Elbaz et al., 2015; Giacoppo et al., 2015b; Gigli et al., 2017; Kalenderoglou et al., 2017; Da Silva et al., 2018; Alharris et al., 2019; Jeong et al., 2019; Winklmayr et al., 2019; Zhang et al., 2019; Łuczaj et al., 2020). The characteristics of these 15 studies are summarised in Appendix 8.

Nine studies were *'in vitro'*, 4 were both *'in vitro'* and animal studies and 2 were animal studies. Mice were the subject used in 5 animal studies and rats were used in 1.

The 9 '*in vitro'* studies demonstrated that CBD:

- Attenuated cell viability of both oestrogen receptor positive and negative cell lines and induced apoptosis in breast cancer cell lines and caused autophagy (Shrivastava et al., 2011).
- Reduced proliferation (Maor et al., 2012; Solinas et al., 2013).
- Downregulated the expression of Kaposi sarcoma related herpesvirus viral G protein coupled receptor (vGPCR), the chemokine growth regulated protein alpha (GRO-α), vascular endothelial growth factor receptor 3 (VEGFR-3), its ligand and growth factor (VEGF-C) (Maor et al., 2012).
- Attenuated the expression of proteins involved in tumour development, invasion and angiogenesis in glioma cells (Solinas et al., 2013).
- Induced apoptosis (Alharris et al., 2019; Winklmayr et al., 2019; Zhang et al., 2019). Yet in the study conducted by Gigli et al., (2017), CBD inhibited apoptosis and cell toxicity.

- Deactivated the mTOR pathway and decreased leukemic cell size (Kalenderoglou et al., 2017).
- Decreased phosphatidylcholine and phosphatidylserine and increased phosphoethanolamine and sphingomyelin (Łuczaj et al., 2020).

The 4 *'in vitro'* and animal studies reported that 'i*n vitro',* CBD promoted apoptosis in gastric cancer. '*In vivo',* CBD prevented tumour growth in the mice (Jeong et al., 2019). CBD did not cause an induction of toxicity nor apoptosis in human umbilical vein endothelial cell (HUVECs). CBD inhibited angiogenesis (Solinas et al., 2012). In breast cancer cells, CBD upregulated extracellular-signal-regulated kinase (ERK) phosphorylation and Id-2 expression and extracellular signal-regulated kinase phosphorylation. CBD inhibited the formation, migration and invasion of triple negative breast cancer cells stimulated by epidermal growth factor (EGF) and prevented tumour growth in the mice models by suppressing tumour cell formation, angiogenic potential and inhibiting the stimulation of EGF receptor, AKT and ERK proteins. CBD inhibited metastasis (McAllister et al., 2011; Elbaz et al., 2015).

The 2 animal studies showed that in the study by Giacoppo et al., (2015b) CBD prevented Fas pathway activation, phospho-ERK p42/44 and cleaved caspase-3 triggering and alterations in mitochondrial permeability (Giacoppo et al., 2015b). In Da Silva et al., (2018), CBD reversed the iron-induced effects and recovered apoptotic proteins (Da Silva et al., 2018).

The impact factor of the 15 articles ranged between 3.24 (PLoS ONE) and 8.469 (Cell Death and Disease) with an average of 5.11.

3.1.5 Cardioprotective effects

Eleven studies reported cardioprotective effects produced by CBD (Rajesh et al., 2010; Walsh et al., 2010; Granjeiro et al., 2011; Ali et al., 2015; Hao et al; 2015; Lee et al., 2016; Jadoon et al., 2017; Wheal et al., 2017; Kossakowski et al., 2019; Baranowska-Kuczko et al., 2020; Sadowska et al., 2020). Their study characteristics are summarised in Appendix 9.

Seven studies were animal studies, 2 were *'in vitro'*, 1 was an *'in vitro'* and an animal study and 1 was a RCT. Rats were used in 5 studies and mice were used in 3 studies.

The 7 animal studies demonstrated that CBD caused a reduction in myocardial dysfunction, cardiac fibrosis, inflammation, oxidative and nitrosative stress, cell death and interrelated signalling pathways (Rajesh et al., 2010; Hao et al., 2015; Lee et al., 2016). Ischaemia-induced ventricular arrhythmias were reduced by CBD (Walsh et al., 2010). CBD reduced inflammation in experimental autoimmune myocarditis (EAM) by attenuating the inflammatory cell invasion and necrosis and CBD improved systolic function and left ventricular myocardium contractility and reversed the EAM-related diastolic dysfunction and myocardial stiffness (Lee et al., 2016). CBD enhanced vasorelaxation in mesenteric arteries and reduced pulmonary hypertension in right ventricular systolic pressure (RVSP) and improved oxygen saturation (Wheal et al., 2017; Sadowska et al., 2020). Conversely, CBD did not induce any significant change on the rats' heart rate and mean arterial pressure (Granjeiro et al., 2011).

The *'in vitro'* and an animal study, demonstrated that CBD increased systolic blood pressure (SBP) and heart rate (HR) and decreased diastolic blood pressure (DBP). In anesthetized rats, single doses of CBD produced dose-dependent reductions in HR, SBP and DBP. In conscious rats, CBD did not have any cardioprotective effects. CBD reduced hypotension, apnoea and bradycardia (Kossakowski et al., 2019).

The 2 *'in vitro'* studies showed that CBD decreased myocyte contractility by suppressing L-type Calcium2+ channels and inhibited excitation-contraction coupling in cardiomyocytes (Ali et al., 2015). CBD produced a concentration-dependent and endothelium-dependent relaxation of human pulmonary arteries and a time-dependent slowly developing decrease in the tone of endothelium-intact human pulmonary arteries (Baranowska-Kuczko et al., 2020). The RCT demonstrated that during stress tests, the 9 healthy participants who received CBD had a reduced systolic and diastolic blood pressure and stroke volume. Cardiac output was maintained and HR was increased (Jadoon et al., 2017).

The impact factor of the 11 articles ranged between 3.533 (Pharmacology Biochemistry and Behaviour) and 24.094 (Journal of the American College of Cardiology) with an average of 7.83.

3.1.6 Other therapeutic effects

Eight studies displayed different potential therapeutic effects of CBD (Rock et al., 2012; Silveira et al., 2014; Stanley et al., 2015; Yeshurun et al., 2015; Toyang et al., 2017; Baban et al., 2018; Palmieri et al., 2019; Salles et al., 2020). The characteristics of these 8 studies are summarised in Appendix 10.

Three studies were animal studies, 2 were *'in vitro'*, 1 was *'in vitro'* and an animal study and 2 studies were clinical trials. Mice were used in the 2 *animal* studies, rats were used in 1 animal study and rats and musk shrews were used in the *'in vitro'* and animal study.

The 3 animal studies reported that CBD reduced the effects of disc injuring induced in rats, produced reno-protective effects in mice and had an effect on acute respiratory distress syndrome (Silveira et al., 2014; Baban et al., 2018; Salles et al., 2020).

The 2 '*in vitro'* studies and the 1 *'in vitro'* and animal study demonstrated that CBD produced an anti-emetic and anti-nausea effect, exhibited direct antiviral activity against hepatitis C but not hepatitis B and produced an acute, non-recoverable vasorelaxation of the human mesenteric arteries (Rock et al., 2012; Stanley et al., 2015; Toyang et al., 2017).

In one of the clinical trials CBD demonstrated that it prevents graft-versus-host-disease (GVHD) in transplant patients and in the other clinical trial CBD demonstrated that it improves psoriasis, skin hydration, elasticity and trans epidermal water loss in various parts of the body (Yeshurun et al., 2015; Palmieri et al., 2019).

The impact factor of the 8 studies ranged between 0.784 (Pharmacognosy Research) and 10.787 (Cardiovascular Research) with an average of 5.17.

3.1.7 Effects on pain

Six studies showed that CBD had an effect on different types of pain (Ward et al., 2011; Ward et al., 2014; Genaro et al., 2017; De Gregorio et al., 2019; Nitecka-Buchta et al., 2019; Anand et al., 2020). The study characteristics are summarised in Appendix 11.

The 6 studies consisted of 1 RCT, 1 *'in vitro'* and 4 animal studies, where mice were used in 2 studies and rats were used in the other 2.

The 4 animal studies reported that CBD had an effect on neuropathic pain (Ward et al., 2011; Ward et al., 2014; Genaro et al., 2017; De Gregorio et al., 2019).

The RCT demonstrated that 70% of the temporomandibular disorder–positive patients who received 20% CBD oil experienced a reduction in pain intensity and 24% of the CBD treated patients experienced a reduction in the masseter muscle activity (Nitecka-Buchta et al., 2019).

The *'in vitro'* study reported that CBD decreased calcium influx in dorsal root ganglion (DRG) neurons treated with capsaicin. CBD attenuated the levels of cyclic adenosine monophosphate (cAMP) and inhibited transient receptor potential vanilloid 1 (TRPV1) signalling (Anand et al., 2020).

The impact factor of the 6 articles ranged between 3.133 (Journal of Pain Research) and 8.739 (British Journal of Pharmacology) with an average of 5.66.

3.1.8 Neuroprotective effects

Five studies demonstrated neuroprotective effects produced by CBD (Liput et al., 2013; Santos et al., 2015; Hind et al., 2016; Sun et al., 2017; Da Silva et al., 2018). The characteristics of these 5 studies are summarised in Appendix 12.

Three studies were '*in vitro'* and 2 were animal studies, where the subjects used were rats.

The 3 *'in vitro'* studies demonstrated that CBD produced neuroprotective effects by increasing cell viability, reducing the activity of caspase-3 and inducing cellular differentiation, reducing cell damage and cell death in neurons and human brain microvascular endothelial cell and human astrocyte co-cultures and protecting hippocampal cells against oxygen-glucose-deprivation/reperfusion induced cytotoxicity (Santos et al., 2015; Hind et al., 2016; Sun et al., 2017).

The 2 animal studies reported that CBD transdermal gel reduced neurodegeneration and CBD restored hippocampal epigenetic modulation of mtDNA (Liput et al., 2013; Da Silva et al., 2018).

The impact factor of the 5 studies ranged between 3.5 (Toxicology in Vitro) and 11.799 (Redox Biology) with an average of 6.76.

3.2 Main findings from the questionnaire for general public

Four hundred participants answered the general public questionnaire (Appendix 1). Table 3.1 demonstrates that 63% of the participants were female, 42% were aged between 26-40 years, 42% had a tertiary level of education and 87% were Maltese.

Table 3.1 Participant demographic data (N=400)

Demographics		**Percentage and number of participants (N=400)**
Gender	Female	62.5% (n=250)
	Male	37.5% (n=150)
Age (years)	18-25	22.3% (n=89)
	26-40	41.5% (n=166)
	41-60	26.8% (n=107)
	60+	9.5% (n=38)
Level of Education	Primary	1.5% (n=6)
	Secondary	8.8% (n=35)
	Post-Secondary	22.3% (n=89)
	Tertiary	41.5% (n=166)
	Post-Tertiary	26% (n=104)
Nationality	Maltese	87.3% (n=349)
	Other	12.8% (n=51)

A sample of 400 respondents selected from the general public aged 18 years and over (approx. 367,000) guarantees a maximum margin of error of 4.9% assuming a 95% confidence level.

3.2.1 Knowledge about CBD

Results demonstrated that prior to participating in the questionnaire, 90% (n=361) of the participants had heard about CBD before. Figure 3.2 demonstrates the sources of information from which participants gained their knowledge of CBD. Seventy-seven percent (n=277) heard and gained their knowledge about CBD from social media/news. Individuals were able to select multiple responses, hence the bar chart adding up to over 100%.

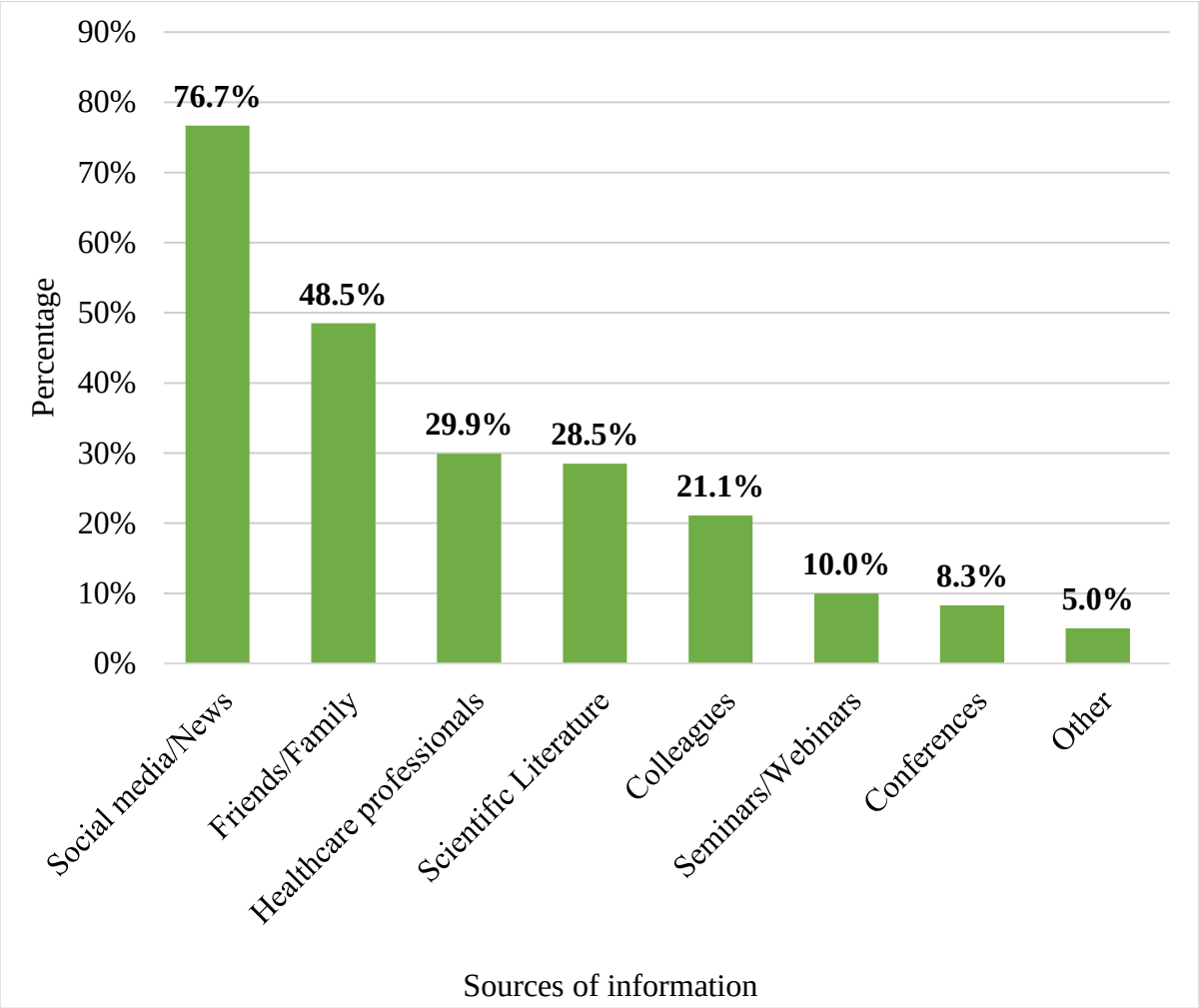

Figure 3.2 Sources of information from which participants gained their knowledge about CBD (N=400)

The other sources of information (5%, n=18) included profession (n=5), internet/individual research (n=5), documentaries/podcasts/films (n=3), personal use (n=2), CBD shops (n=2) and school (n=1).

Seventy-one percent (n=283) of the participants discussed the use and effects of CBD, 88% (n=247) of which discussed the use and effects of CBD with friends/family.

Table 3.2 demonstrates that the largest mean rating score is 4.22 of S.5 indicating the highest agreement. The mean rating scores provided to the statements vary significantly since the p-value (approx. 0) is less than the 0.05 criterion. This can be observed in Figure 3.4.

Table 3.2 Statements assessing the knowledge about CBD

Statements	**Mean**	**Std. Deviation**
S.1: CBD and THC are naturally occurring compounds derived from cannabis	4.16	0.889
S.2: CBD and THC produce different biological effects because they work differently	3.97	0.943
S.3: CBD has a lower risk of producing mental effects compared to THC	3.73	0.993
S.4: In humans, CBD is converted to THC	2.53	0.895
S.5: CBD available in several formulations	4.22	0.955
S.6: Legality of CBD in the EU is unclear	3.47	1.026
S.7: Dosing depends on weight, but there is no standard dose	3.68	0.920
S.8: CBD products do not interact with other medications	2.77	0.963
S.9: Stopping the use of CBD might produce withdrawal symptoms	2.77	1.074
S.10: CBD can cause a euphoric/high sensation	2.47	1.124

$X^2(9) = 1320.65$, $p < 0.001$

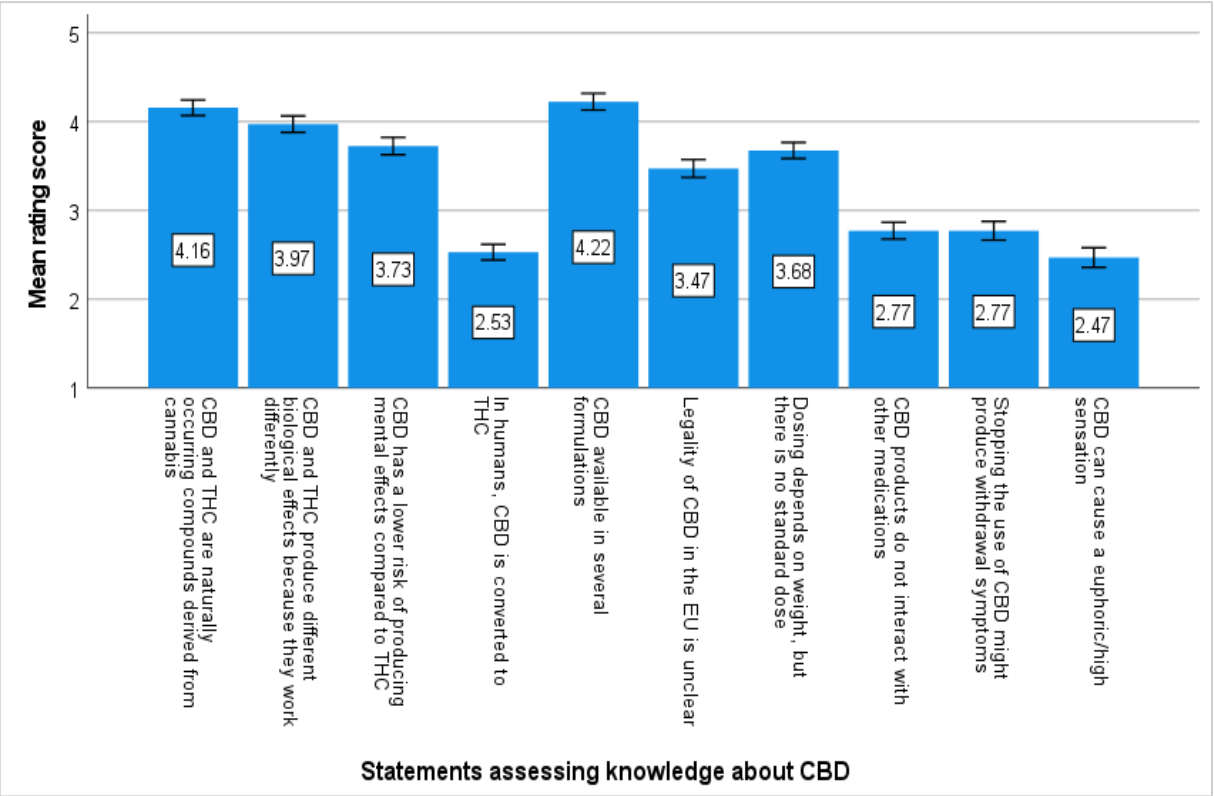

Figure 3.3 Error bar graph displaying the mean rating scores of the statements (N=400)

Table 3.3 shows that the mean rating scores provided to every statement, except of statement 4 (p-value = 0.331) and statement 9 (p-value = 0.770), vary significantly between the groups since the p-value is less than the 0.05 level of significance.

Table 3.3 Kruskal Wallis test result between the provided statements and age (N=400)

	Age	Sample size	Mean	Std. Dev	P-value
S.1: CBD and THC are naturally occurring compounds derived from cannabis	18-25	89	4.39	0.685	<0.001
	26-40	166	4.32	0.771	
	41-60	107	4.01	0.976	
	60+	38	3.32	0.989	
S.2: CBD and THC produce different biological effects because they work differently	18-25	89	4.18	0.806	<0.001
	26-40	166	4.10	0.868	
	41-60	107	3.88	1.016	
	60+	38	3.21	0.963	
S.3: CBD has a lower risk of producing mental effects compared to THC	18-25	89	3.96	0.852	<0.001
	26-40	166	3.90	0.909	
	41-60	107	3.49	1.093	
	60+	38	3.08	0.969	
S.5: CBD available in several formulations	18-25	89	4.48	0.725	<0.001
	26-40	166	4.45	0.798	
	41-60	107	4.02	1.046	
	60+	38	3.24	1.051	
S.6: Legality of CBD in the EU is unclear	18-25	89	3.57	0.976	0.034
	26-40	166	3.55	1.006	
	41-60	107	3.41	1.064	
	60+	38	3.05	1.038	
S.7: Dosing depends on weight, but there is no standard dose	18-25	89	3.81	0.928	<0.001
	26-40	166	3.80	0.820	
	41-60	107	3.58	0.962	
	60+	38	3.11	0.981	
S.8: CBD products do not interact with other medications	18-25	89	2.53	0.918	0.009
	26-40	166	2.92	1.012	
	41-60	107	2.74	0.935	
	60+	38	2.82	0.834	
S.10: CBD can cause a euphoric/high sensation	18-25	89	2.48	1.216	0.046
	26-40	166	2.39	1.089	
	41-60	107	2.42	1.158	
	60+	38	2.92	0.850	

The mean rating scores in Table 3.4 demonstrate that the mean rating score for each individual statement except for statements 6 (p-value = 0.998), 7 (p-value = 0.783) and 8 (p-value = 0.578), differ significantly. The alternative hypothesis is accepted since the p-values are less than the 0.05 criterion.

Table 3.4 Kruskal Wallis test result between the provided statements and nationality (N=400)

	Nationality	**Sample size**	**Mean**	**Std. Dev**	**P-value**
S.1: CBD and THC are naturally occurring compounds derived from cannabis	Maltese	349	4.11	0.886	<0.001
	Other	51	4.51	0.834	
S.2: CBD and THC produce different biological effects because they work differently	Maltese	349	3.90	0.936	<0.001
	Other	51	4.45	0.856	
S.3: CBD has a lower risk of producing mental effects compared to THC	Maltese	349	3.69	0.966	0.018
	Other	51	3.98	1.140	
S.4: In humans, CBD is converted to THC	Maltese	349	2.56	0.851	0.014
	Other	51	2.29	1.137	
S.5: CBD available in several formulations	Maltese	349	4.19	0.957	0.006
	Other	51	4.49	0.903	
S.9: Stopping the use of CBD might produce withdrawal symptoms	Maltese	349	2.82	1.057	0.012
	Other	51	2.43	1.136	
S.10: CBD can cause a euphoric/high sensation	Maltese	349	2.52	1.113	0.026
	Other	51	2.16	1.155	

The mean rating scores in Table 3.5 demonstrate that the mean rating score for each individual statement except for statement 8 (p-value = 0.516), differ significantly. The alternative hypothesis is accepted since the p-value is less than the 0.05 level of significance. The results of the Kruskal Wallis test between the provided statements and the demographical group being gender did not show significant differences between the mean rating scores since the p-value exceeded the 0.05 level of significance.

Table 3.5 Kruskal Wallis test result between the provided statements and whether participants heard about CBD (N=400)

	Heard about CBD	Sample size	Mean	Std. Dev.	P-value
S.1: CBD and THC are naturally occurring compounds derived from cannabis	Yes	361	4.24	0.870	<0.001
	No	39	3.36	0.628	
S.2: CBD and THC produce different biological effects because they work differently	Yes	361	4.06	0.927	<0.001
	No	39	3.13	0.615	
S.3: CBD has a lower risk of producing mental effects compared to THC	Yes	361	3.79	1.003	<0.001
	No	39	3.13	0.656	
S.4: In humans, CBD is converted to THC	Yes	361	2.48	0.919	<0.001
	No	39	2.95	0.456	
S.5: CBD available in several formulations	Yes	361	4.32	0.934	<0.001
	No	39	3.38	0.711	
S.6: Legality of CBD in the EU is unclear	Yes	361	3.51	1.044	0.003
	No	39	3.13	0.767	
S.7: Dosing depends on weight, but there is no standard dose	Yes	361	3.72	0.931	<0.001
	No	39	3.23	0.667	
S.9: Stopping the use of CBD might produce withdrawal symptoms	Yes	361	2.74	1.092	0.047
	No	39	3.08	0.839	
S.10: CBD can cause a euphoric/high sensation	Yes	361	2.41	1.142	<0.001
	No	39	3.00	0.761	

Table 3.6 demonstrates that there is a larger percentage of participants aged between 18-25 (96.6%) than the other ages who have heard about CBD before. These percentage differences are significant since the p-value (<0.001) is less than the 0.05 level of significance. Table 3.7 shows that there is a larger percentage of participants who are knowledgeable about CBD (98.9%) than those who are not knowledgeable (69.2%) who believe that CBD has a therapeutic effect.

The results of the Chi-square test performed to assess the association between nationality and whether the participant had heard about CBD did not show statistical significance as the p-value (0.319) exceeded the 0.05 level of significance.

Table 3.6 Chi-square test for knowledge about CBD and age (N=400)

			Have you heard about CBD?	
			Yes	**No**
Age	**18-25**	Percentage	96.6%	3.4%
	26-40	Percentage	94.0%	6.0%
	41-60	Percentage	89.7%	10.3%
	60+	Percentage	60.5%	39.5%

$X^2(3) = 44.92$, $p = <0.001$

Table 3.7 Chi-square test for knowledge about CBD and if CBD has a therapeutic effect (N=400)

			CBD has a therapeutic effect	
			Yes	**No**
Have you heard about CBD?	**Yes**	Percentage	98.9%	1.1%
	No	Percentage	69.2%	30.8%

$X^2(1) = 80.64$, $p = <0.001$

Ninety-six percent (n=384) of the participants agree that CBD has a therapeutic effect. Tables 3.8, 3.9 and 3.10 demonstrate that there is a larger percentage of females (98.4%), participants aged between 26-40 (98.2%) and participants who have a tertiary level of education (98.8%) who believe that CBD has a therapeutic effect. These percentage differences are significant since the p-values are less than the 0.05 level of significance. The association between this categorical variable and nationality was not statistically significant as the p-value (0.119) exceeded the 0.05 level of significance.

Table 3.8 Chi-square test for gender and whether CBD has a therapeutic effect (N=400)

			CBD has a therapeutic effect	
			Yes	**No**
Gender	**Female**	Percentage	98.4%	1.6%
	Male	Percentage	92.0%	8.0%

$X^2(1) = 10.00$, $p = 0.002$

Table 3.9 Chi-square test between age and whether CBD has a therapeutic effect (N=400)

			CBD has a therapeutic effect	
			Yes	**No**
Age	**18-25**	Percentage	97.8%	2.2%
	26-40	Percentage	98.2%	1.8%
	41-60	Percentage	96.3%	3.7%
	60+	Percentage	81.6%	18.4%

$X^2(3) = 23.39$, p = <0.001

Table 3.10 Chi-square test between education and whether CBD has a therapeutic effect (N=400)

			CBD has a therapeutic effect	
			Yes	**No**
Level of Education	**Primary**	Percentage	83.3%	16.7%
	Secondary	Percentage	82.9%	17.1%
	Post-secondary	Percentage	94.4%	5.6%
	Tertiary	Percentage	98.8%	1.2%
	Post-tertiary	Percentage	98.1%	1.9%

$X^2(4) = 23.40$, p = <0.001

Table 3.11 demonstrates that 78% (n=314) of the participants believe that CBD has an analgesic effect, 1.5% (n=6) of the participants do not know if CBD has any therapeutic effects and 1.3% (n=5) believe that CBD has no therapeutic effects. In this question individuals were able to select multiple responses, hence the frequency and percentage adding up to over 400 and 100% respectively.

Table 3.11 Potential therapeutic effects of CBD according to the participants (N=400)

Potential therapeutic effects of CBD	**Frequency**	**Percentage**
Antipsychotic	116	29.0%
Antitumour	98	24.5%
Anxiolytic	305	76.3%
Anti-inflammatory	192	48.0%
Antiepileptic	180	45.0%
Anti-vomiting	66	16.5%
Antioxidant	76	19.0%
Antidepressant	220	55.0%
Cardioprotective	53	13.3%
Neuroprotective	60	15.0%
Pain killer	314	78.5%
Other	8	2.0%
I do not know	6	1.5%
None	5	1.3%

Eight participants mentioned other therapeutic effects that CBD can cause, which are the following:

- Promote and improve sleep (n=3)
- Value expressive (n=1)
- Increase in weight (n=1)
- Effective in autism, attention deficit hyperactivity disorder, irritable bowel syndrome, migraines, endometriosis, constipation (n=1)
- Effective in Parkinson's disease and cerebral palsy (n=1)
- Effective in arthritis, Crohn's disease, diabetes, multiple sclerosis, cancer treatment, anxiety, general pain and brain health (n=1).

Results demonstrated that 45% (n=180) of the participants believe that CBD causes sedation and drowsiness, 4% (n=15) of the participants do not know if CBD has any side effects and 8% (n=32) believe that CBD has no side effects.

Nine participants stated that CBD can cause other side effects or responded with different opinions, which are the following:

- Drug to drug interactions (n=2)
- Addiction (n=1)
- Long term mental side effects (n=1)
- Heightened emotions (n=1)
- Physical side effects (n=1)
- Dental problems (n=1)
- CBD has little known side effects (n=1)
- Anti-aging effect (n=1)

Participants who are knowledgeable about CBD had a larger percentage (8.3%) for believing that CBD does not cause side effects. Participants who are not knowledgeable about CBD, had a larger percentage (12.8%) for not knowing if CBD causes side effects. These percentage differences are significant since the p-value (0.004) is less than the 0.05 level of significance.

3.2.2 Perceptions of CBD

Eighty-six percent (n=342) of the participants believe that CBD products should be accessible in Malta for medicinal use, while 2% (n=6) do not believe with this statement. Thirteen percent (n=52) were unsure whether CBD products should be accessible in Malta.

Tables 3.12, 3.13 and 3.14 demonstrate that participants aged between 26-40 years (91.0%), participants with a tertiary level of education (89.8%) and participants who believe that CBD has a therapeutic effect (88.0%), respectively, believe that CBD products intended for medicinal use should be available in Malta. These percentage differences are significant since the p-value (<0.001) is less than the 0.05 level of significance.

There were no statistical associations between accessibility of CBD in Malta and gender ($p = 0.355$) and nationality ($p = 0.289$) as the p-values exceeded the 0.05 level of significance.

Table 3.12 Chi-square test for age and accessibility of CBD products in Malta (N=400)

			Do you think that CBD products intended for medicinal use, should be legally available in Malta?		
			Yes	**No**	**Not sure**
Age	**18-25**	Percentage	89.9%	0.0%	10.1%
	26-40	Percentage	91.0%	1.2%	7.8%
	41-60	Percentage	85.0%	1.9%	13.1%
	60+	Percentage	52.6%	7.9%	39.5%

$X^2(6) = 40.56$, $p = < 0.001$

Table 3.13 Chi-square test for education and accessibility of CBD products in Malta (N=400)

			Do you think that CBD products intended for medicinal use, should be legally available in Malta?		
			Yes	**No**	**Not sure**
Level of Education	**Primary**	Percentage	33.3%	33.3%	33.3%
	Secondary	Percentage	74.3%	0.0%	25.7%
	Post-secondary	Percentage	84.3%	1.1%	14.6%
	Tertiary	Percentage	89.8%	1.2%	9.0%
	Post-tertiary	Percentage	86.5%	1.9%	11.5%

$X^2(8) = 46.88$, $p = < 0.001$

Table 3.14 Chi-square test between accessibility of CBD products in Malta and whether CBD has a therapeutic effect (N=400)

			Do you think that CBD products intended for medicinal use, should be legally available in Malta?		
			Yes	**No**	**Not sure**
CBD has a therapeutic effect	**Yes**	Percentage	88.0%	1.6%	10.4%
	No	Percentage	25.0%	6.3%	68.8%

$X^2(2) = 50.06$, $p = <0.001$

Fifty-one percent (n=202) of the participants believe that if CBD products were to be legally available in Malta, they should be classified as POM. Twenty-one percent (n=84) of the participants believe that CBD products may be bought from retail shops such as health shops.

Table 3.15 demonstrates that there are larger percentages of participants who do not believe or are not sure that CBD products should accessible in Malta (3.0% and 22.3%) who perceive that if CBD products were accessible in Malta, they should be POM. These percentage differences are significant since the p-value (<0.001) is less than the 0.05 level of significance.

Table 3.16 shows a larger percentage of participants who are not knowledgeable about CBD (84.6%) than those who are (46.8%) who believe that CBD products should be POM. These percentage differences are significant since the p-value (<0.001) is less than the 0.05 level of significance.

There were no statistical associations between classification of CBD products and gender (p = 0.410), age (p = 0.147), education (p = 0.102) and whether CBD has a therapeutic effect (p = 0.119) as the p-values exceeded the 0.05 level of significance.

Table 3.15 Chi-square test for classification and accessibility of CBD products in Malta (N=400)

			Do you think that CBD products intended for medicinal use, should be legally available in Malta?		
			Yes	**No**	**Not sure**
Classification	**POM**	Percentage	74.8%	3.0%	22.3%
	OTC	Percentage	93.9%	0.9%	5.3%
	General sales	Percentage	100.0%	0.0%	0.0%

$X^2(4) = 39.51$, p = <0.001

Table 3.16 Chi-square test for knowledge about CBD and classification of CBD products (N=400)

			If CBD products (e.g., oils, capsules) were to be legally available in Malta, which category do you think they should be classified in?		
			POM	**OTC**	**General sales**
Have you heard about CBD?	**Yes**	Percentage	46.8%	30.5%	22.7%
	No	Percentage	84.6%	10.3%	5.1%

$X^2(2) = 20.19$, $p = <0.001$

Table 3.17 demonstrates that the largest mean rating score is 4.22 of S.11 indicating the highest agreement. The mean rating scores provided to the statements vary significantly since the p-value (approx. 0) is less than the 0.05 criterion. The error bar graph in Figure 3.4 exhibits slight overlapping of confidence interval indicating that the mean rating scores differ significantly.

Table 3.17 Statements assessing the perceptions about CBD (N=400)

Statements	Mean	Std. Dev
S.1: CBD products available in health shops and pharmacies are of the same quality, safety and efficacy	3.15	1.294
S.2: Potential use of CBD might cause judgement or conflicts between healthcare professionals and patients	3.34	1.028
S.3: CBD products should not be used due to potential impairing effects on driving	2.51	1.135
S.4: CBD should only be legally available in pharmacies	3.47	1.356
S.5: CBD should be legally available in health shops, grocery shops and other retail shop	2.47	1.387
S.6: CBD products recommended or prescribed by a healthcare professional (e.g., pharmacist, physician, nurse) are more likely to be used by patients	3.91	.950
S.7: CBD products should be used in preference to conventional medicine	3.04	1.154
S.8: CBD products should be used for minor ailments (e.g., headache, joint pain, minor sleep disorders)	3.25	1.274
S.9: CBD products should be used for major medical conditions (e.g., mental illness, epilepsy, cancer)	3.78	1.050
S.10: CBD should be classified as dangerous or harmful	2.11	1.149
S.11: Healthcare professionals should be able to recommend or prescribe CBD products	4.22	.853
S.12: CBD products intended for medicinal use should only be considered if there is no viable alternative medicine	2.58	1.248
S.13: CBD is very safe and has minimal side effects since it is a naturally occurring compound derived from cannabis	3.53	1.073
S.14: CBD use can lead to the use of more dangerous drugs (e.g., cocaine, heroin)	2.03	1.126
S.15: CBD products used for recreational purposes should be decriminalised	3.46	1.352

X^2 (14) = 1383.87, $p < 0.001$

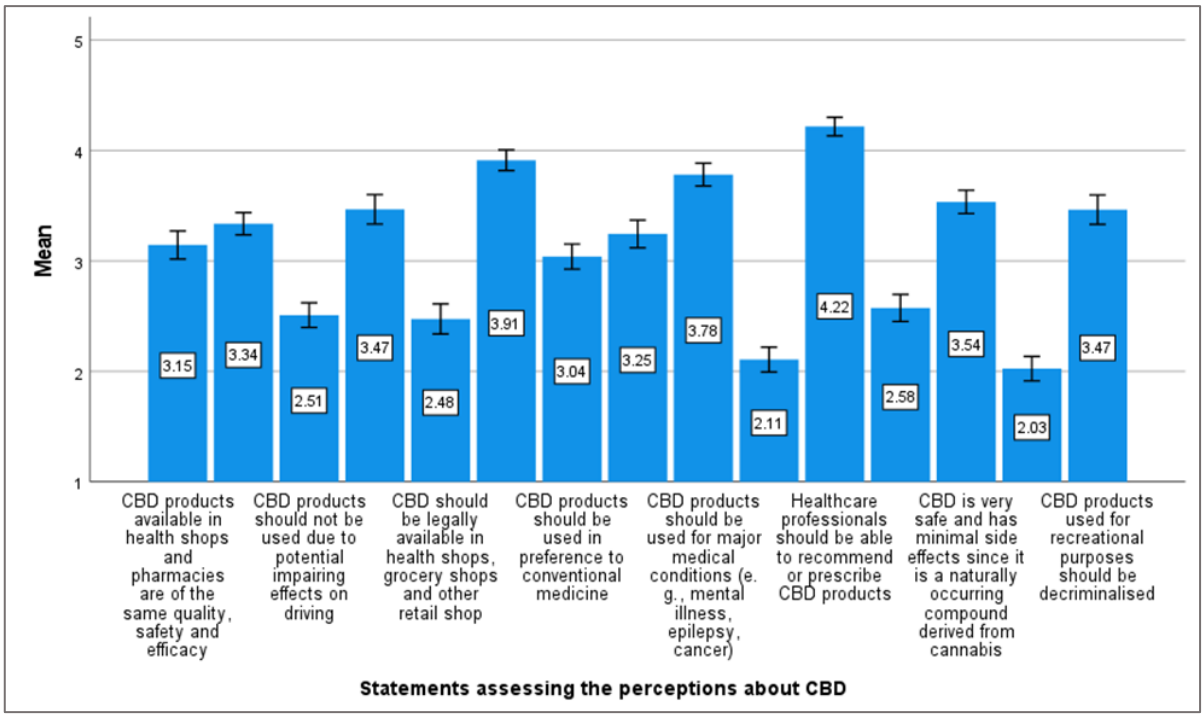

Figure 3.4 Error bar graph demonstrating the mean rating scores of the statements (N=400)

The mean rating scores in Table 3.18 shows that the mean rating scores provided to statement 5 till 15 vary significantly between the groups since the p-value is less than the 0.05 level of significance.

Table 3.18 Kruskal Wallis test result between the provided statements and age (N=400)

	Age	Sample size	Mean	Std. Dev	P-value
S.5: CBD should be legally available in health shops, grocery shops and other retail shop	18-25	89	2.33	1.286	0.050
	26-40	166	2.71	1.440	
	41-60	107	2.31	1.410	
	60+	38	2.26	1.201	
S.6: CBD products recommended or prescribed by a healthcare professional are more likely to be used by patients	18-25	89	4.15	0.806	0.010
	26-40	166	3.95	0.942	
	41-60	107	3.77	1.005	
	60+	38	3.63	1.025	
S.7: CBD products should be used in preference to conventional medicine	18-25	89	3.10	1.088	0.002
	26-40	166	3.13	1.109	
	41-60	107	3.09	1.233	
	60+	38	2.34	1.072	
S.8: CBD products should be used for minor ailments (e.g., headache, joint pain, minor sleep disorders)	18-25	89	3.22	1.250	0.008
	26-40	166	3.48	1.220	
	41-60	107	3.06	1.323	
	60+	38	2.82	1.270	
S.9: CBD products should be used for major medical conditions (e.g., mental illness, epilepsy, cancer)	18-25	89	3.89	1.038	0.005
	26-40	166	3.89	0.960	
	41-60	107	3.73	1.060	
	60+	38	3.21	1.255	
S.10: CBD should be classified as dangerous or harmful	18-25	89	1.91	0.900	<0.001
	26-40	166	1.93	1.178	
	41-60	107	2.24	1.140	
	60+	38	2.97	1.150	
S.11: Healthcare professionals should be able to recommend or prescribe CBD products	18-25	89	4.26	0.819	<0.001
	26-40	166	4.37	0.750	
	41-60	107	4.07	0.978	
	60+	38	3.84	0.823	
S.12: CBD products intended for medicinal use should only be considered if there is no viable alternative medicine	18-25	89	2.52	1.035	<0.001
	26-40	166	2.30	1.167	
	41-60	107	2.72	1.372	
	60+	38	3.53	1.202	
S.13: CBD is very safe and has minimal side effects since it is a naturally occurring compound derived from cannabis	18-25	89	3.51	1.024	0.043
	26-40	166	3.69	1.038	
	41-60	107	3.44	1.134	
	60+	38	3.21	1.094	
S.14: CBD use can lead to the use of more dangerous drugs (e.g., cocaine, heroin)	18-25	89	1.94	0.946	<0.001
	26-40	166	1.70	0.942	
	41-60	107	2.24	1.250	
	60+	38	3.00	1.230	
S.15: CBD products used for recreational purposes should be decriminalised	18-25	89	3.69	1.258	<0.001
	26-40	166	3.73	1.251	
	41-60	107	3.13	1.401	
	60+	38	2.71	1.412	

The results of the Kruskal Wallis test between the provided statements and the categorical group being knowledge about CBD showed significant differences between the mean rating scores of nine statements since the p-value is less than the 0.05 level of significance (Table 3.19).

The results of the Kruskal Wallis test between the provided statements and the demographical group being gender and education did not show significant differences between the mean rating scores since the p-value exceeded the 0.05 level of significance.

Table 3.19 Kruskal Wallis test result between the provided statements and knowledge about CBD (N=400)

	Heard about CBD	Sample size	Mean	Std. Dev	P-value
S.3: CBD products should not be used due to potential impairing effects on driving	Yes	361	2.41	1.112	<0.001
	No	39	3.41	0.938	
S.6: CBD products recommended or prescribed by a healthcare professional (e.g., pharmacist, physician, nurse) are more likely to be used by patients	Yes	361	3.95	0.946	0.010
	No	39	3.59	0.938	
S.9: CBD products should be used for major medical conditions (e.g., mental illness, epilepsy, cancer)	Yes	361	3.82	1.034	0.019
	No	39	3.41	1.141	
S.10: CBD should be classified as dangerous or harmful	Yes	361	2.03	1.148	<0.001
	No	39	2.82	0.885	
S.11: Healthcare professionals should be able to recommend or prescribe CBD products	Yes	361	4.29	0.829	<0.001
	No	39	3.59	0.818	
S.12: CBD products intended for medicinal use should only be considered if there is no viable alternative medicine	Yes	361	2.48	1.241	<0.001
	No	39	3.41	0.993	
S.13: CBD is very safe and has minimal side effects since it is a naturally occurring compound derived from cannabis	Yes	361	3.58	1.096	0.002
	No	39	3.15	0.745	
S.14: CBD use can lead to the use of more dangerous drugs (e.g., cocaine, heroin	Yes	361	1.91	1.076	<0.001
	No	39	3.13	0.978	
S.15: CBD products used for recreational purposes should be decriminalised	Yes	361	3.55	1.349	<0.001
	No	39	2.72	1.146	

The mean rating scores in Table 3.20 shows that the mean rating scores provided to every statement, except for statement 2 (p-value = 0.068) and 6 (p-value = 0.108), vary significantly between the groups since the p-value is less than the 0.05 level of significance.

Table 3.20 Kruskal Wallis test result between the provided statements and accessibility of CBD products in Malta (N=400)

	CBD should be available in Malta	**Sample size**	**Mean**	**Std. Dev**	**P-value**
S.1: CBD products available in health shops and pharmacies are of the same quality, safety and efficacy	Yes	342	3.25	1.284	<0.001
	No	7	2.14	1.215	
	Not sure	51	2.59	1.186	
S.3: CBD products should not be used due to potential impairing effects on driving	Yes	342	2.31	1.026	<0.001
	No	7	4.86	0.378	
	Not sure	51	3.53	0.987	
S.4: CBD should only be legally available in pharmacies	Yes	342	3.37	1.398	0.005
	No	7	4.57	0.535	
	Not sure	51	3.94	0.925	
S.5: CBD should be legally available in health shops, grocery shops and other retail shop	Yes	342	2.61	1.407	<0.001
	No	7	1.00	0.000	
	Not sure	51	1.78	0.966	
S.7: CBD products should be used in preference to conventional medicine	Yes	342	3.13	1.136	<0.001
	No	7	1.86	1.574	
	Not sure	51	2.57	1.025	

Table 3.20 Kruskal Wallis test result between the provided statements and accessibility of CBD products in Malta (N=400)

S.8: CBD products should be used for minor ailments (e.g., headache, joint pain, minor sleep disorders)	Yes	342	3.39	1.241	<0.001
	No	7	1.86	1.069	
	Not sure	51	2.47	1.138	
S.9: CBD products should be used for major medical conditions (e.g., mental illness, epilepsy, cancer)	Yes	342	3.88	1.009	<0.001
	No	7	2.57	1.813	
	Not sure	51	3.31	0.990	
S.10: CBD should be classified as dangerous or harmful	Yes	342	1.89	1.025	<0.001
	No	7	3.57	1.618	
	Not sure	51	3.33	0.952	
S.11: Healthcare professionals should be able to recommend or prescribe CBD products	Yes	342	4.33	0.809	<0.001
	No	7	4.29	0.756	
	Not sure	51	3.47	0.784	
S.12: CBD products intended for medicinal use should only be considered if there is no viable alternative medicine	Yes	342	2.40	1.194	<0.001
	No	7	4.14	1.464	
	Not sure	51	3.53	0.987	
S.13: CBD is very safe and has minimal side effects since it is a naturally occurring compound derived from cannabis	Yes	342	3.67	1.035	<0.001
	No	7	2.00	1.000	
	Not sure	51	2.82	0.888	
S.14: CBD use can lead to the use of more dangerous drugs (e.g., cocaine, heroin	Yes	342	1.82	0.987	<0.001
	No	7	3.57	1.813	
	Not sure	51	3.18	1.053	
S.15: CBD products used for recreational purposes should be decriminalised	Yes	342	3.62	1.332	<0.001
	No	7	2.00	1.528	
	Not sure	51	2.65	1.036	

Figure 3.5 demonstrates that 53% (n=210) of the participants agree to strongly agree that potential use of CBD might cause judgement or conflicts between healthcare professionals and patients.

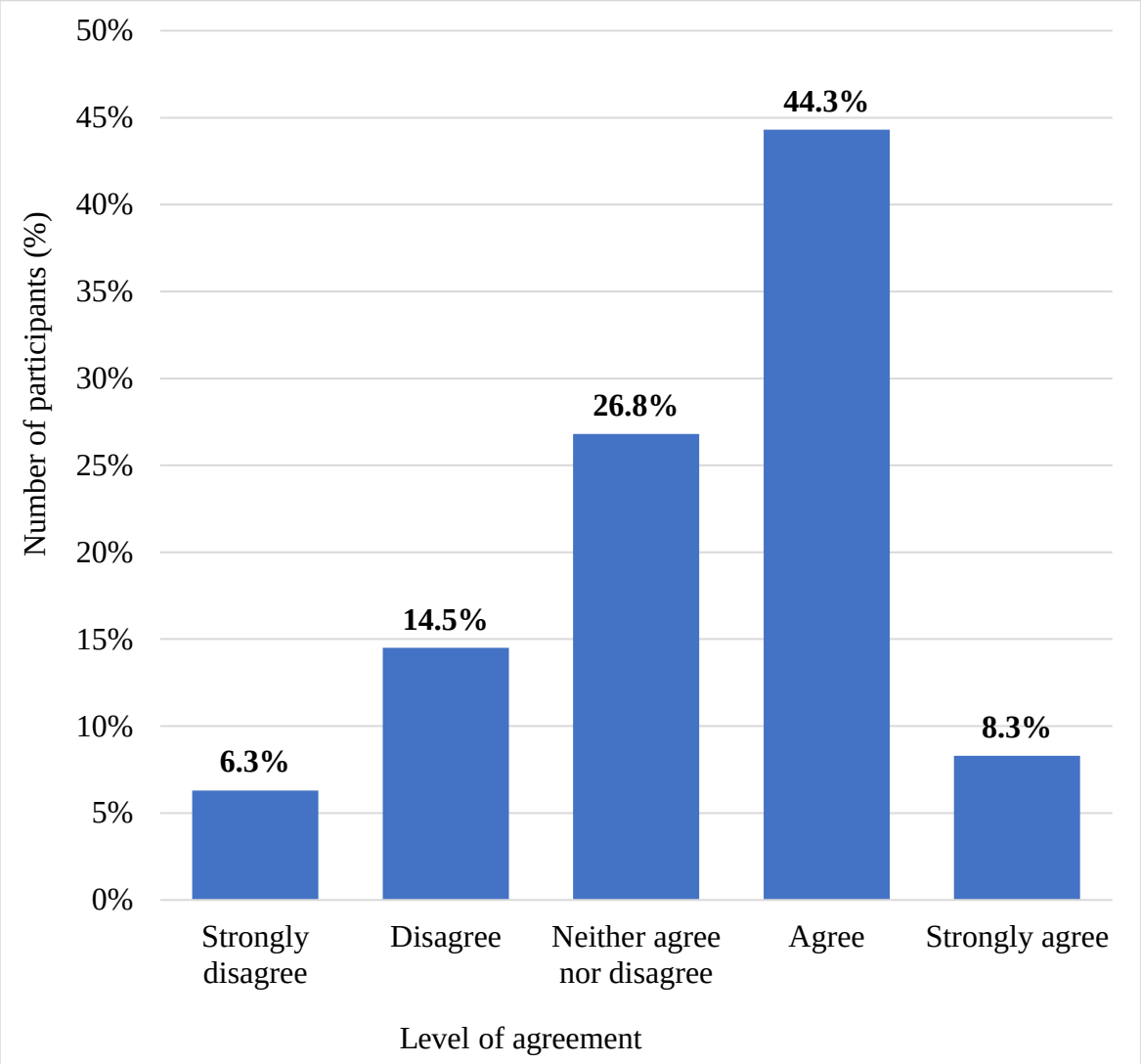

Figure 3.5 Potential use of CBD products might cause judgement (N=400)

Figure 3.6 shows that 77% (n=306) of the participants believe that CBD products recommended or prescribed by a healthcare professional (e.g., pharmacist, physician, nurse) are more likely to be used by patients.

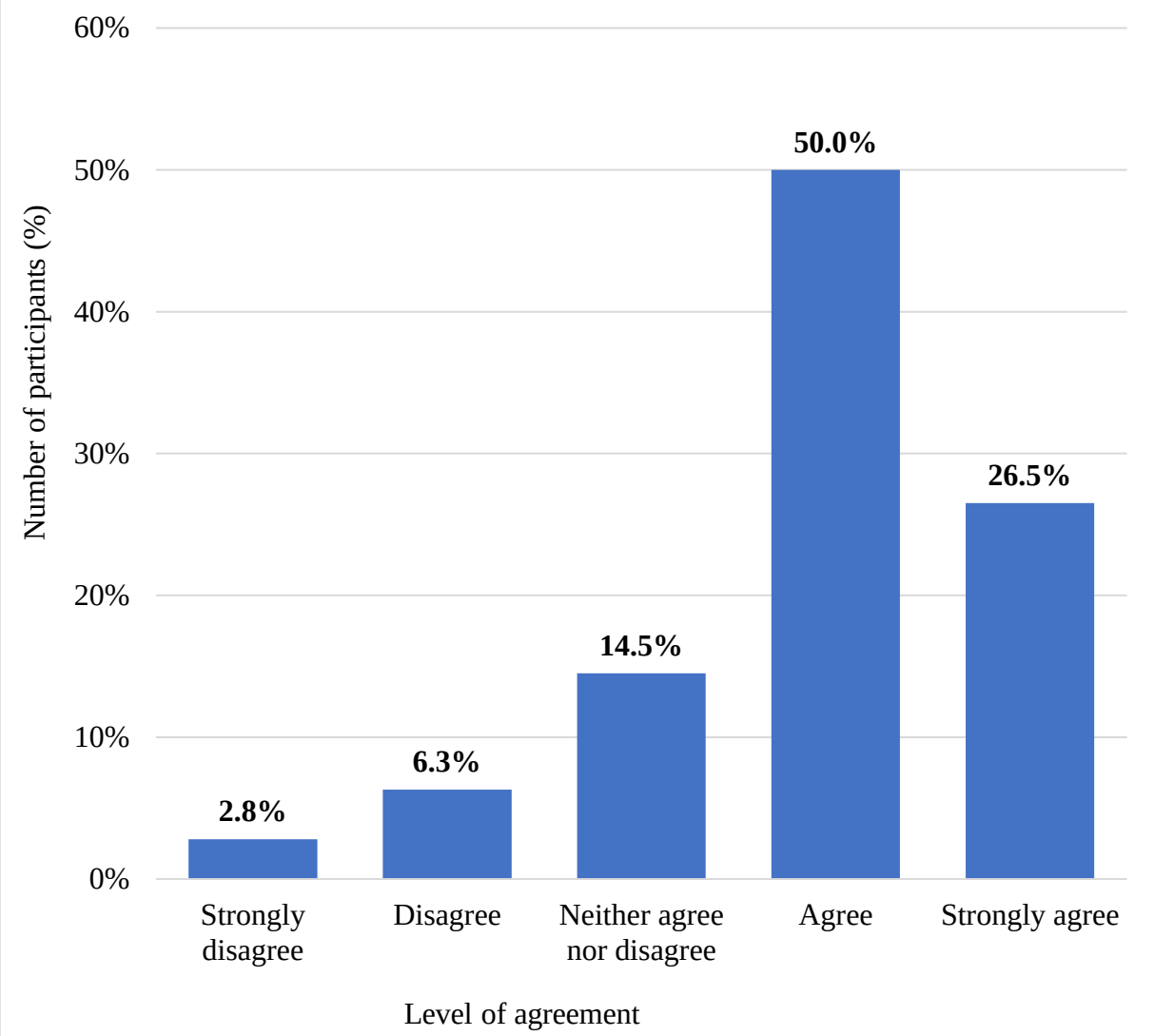

Figure 3.6 Likelihood of CBD products being used by patients (N=400)

3.2.3 Barriers related to CBD

Figure 3.7 demonstrates that 66% (n=262) of the participants believe that if CBD were to be legally available in Malta, social stigma associated with the use of CBD for medicinal use would pose as the highest potential barrier. Individuals were able to select multiple responses, hence the bar chart adding up to over 100%.

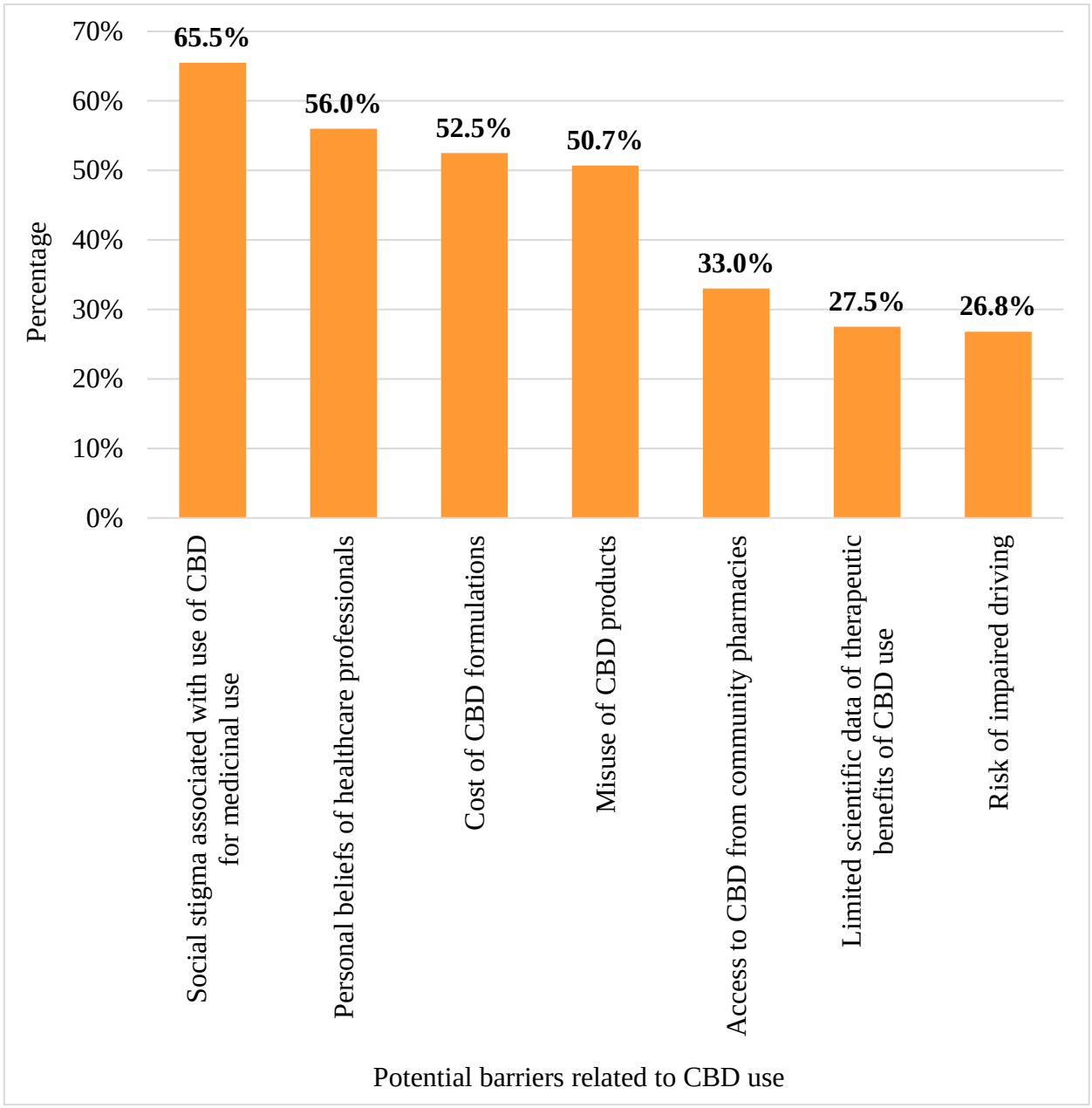

Figure 3.7 Potential barriers related to CBD use (N=400)

3.3 Main findings from the questionnaire for healthcare professionals

One hundred and fifty individuals answered the questionnaire for healthcare professionals (Appendix 1). Table 3.21 demonstrates that 59% of the healthcare professionals were female, 53% were aged between 26-40 years, 51% had a post-tertiary level of education, 91% were Maltese, 49% were pharmacists and 43% had 1-5 years of practice.

A sample of 150 respondents selected from healthcare professionals aged 18 years and over (approx. 12,700) guarantees a maximum margin of error of 7.95% assuming a 95% confidence level.

Table 3.21 Participant demographic data (N=150)

Demographics		**Percentage and number of participants (N=150)**
Gender	Female	58.7% (n=88)
	Male	41.3% (n=62)
Age (years)	18-25	22% (n=33)
	26-40	52.7% (n=79)
	41-60	21.3% (n=32)
	60+	4% (n=6)
Level of Education	Primary	0
	Secondary	0
	Post-Secondary	1.3% (n=2)
	Tertiary	48% (n=72)
	Post-Tertiary	50.7% (n=76)
Nationality	Maltese	90.7% (n=136)
	Other	9.3% (n=14)
Healthcare Profession	Dentist	0.7% (n=1)
	Medical Doctor	22.7% (n=34)
	Midwife	0.7% (n=1)
	Nurse	8.0% (n=12)
	Pharmacist	48.7% (n=73)
	Pharmacy Technician	2.7% (n=4)
	Physiotherapist	2.0% (n=3)
	Podiatrist	6.7% (n=10)
	Psychologist	4.7% (n=7)
	Radiographer	1.3% (n=2)
	Scientist	1.3% (n=2)
	Veterinarian	0.7% (n=1)
Years of Practice	1-5	42.7% (n=64)
	6-10	19.3% (n=29)
	11-20	15.3% (n=23)
	21-30	11.3% (n=17)
	>30	11.3% (n=17)

3.3.1 Knowledge about CBD

Results demonstrated that prior to participating in the questionnaire, 97% (n=146) of healthcare professionals had heard about CBD before. Figure 3.8 demonstrates the sources of information from which healthcare professionals gained their knowledge of CBD.

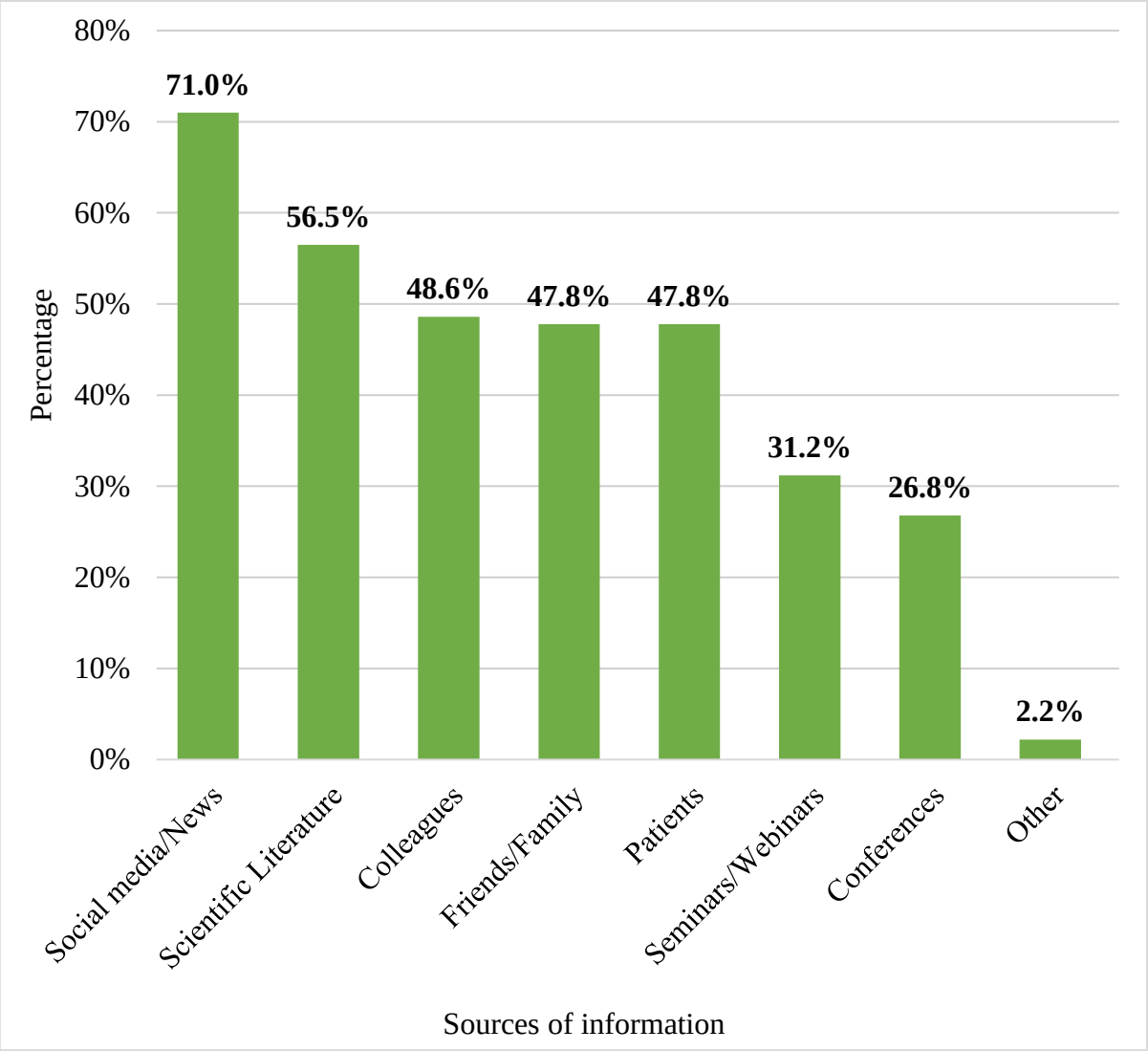

Figure 3.8 Sources of information from which healthcare professionals gained their knowledge about CBD (N=150)

Ninety-eight healthcare professionals heard and gained their knowledge about CBD from social media/news. Individuals were able to select multiple responses, hence the bar chart adding up to over 100%. Other sources of information (2.2%, n=3) included gaining information through medical representatives (n=1), documentaries (n=1) and through past work experience (n=1).

Sixty-one percent (n=91) of healthcare professionals had patients asking them about CBD and its use, with pharmacists (n=52) having had more patients asking them about CBD and its use.

Table 3.22 demonstrates that the largest mean rating score is 2.52 of S.17 indicating the highest knowledge out of all the provided statements. The mean rating scores provided to the statements vary significantly since the p-value (approx. 0) is less than the 0.05 criterion. The error bar graph in Figure 3.9 exhibits demonstrates slight overlapping of the confidence intervals which further indicates that the mean rating scores differ significantly.

Table 3.22 Statements assessing the knowledge of healthcare professionals about CBD

Statements	Mean	Std. Deviation
S.1: Mechanism of action of CBD	2.09	0.951
S.2: Mechanism of action of THC	2.01	0.966
S.3: Different biological effects of CBD and THC	2.21	1.001
S.4: Different toxic effects of CBD and THC	2.12	1.003
S.5: Different therapeutic effects of CBD and THC	2.21	0.971
S.6: EMA approved indications	1.83	0.995
S.7: FDA approved indications	1.65	0.956
S.8: Ratio of Bediol®	1.89	1.344
S.9: Ratio of Bedrocan®	1.92	1.344
S.10: Ratio of Pedanios 20/1®	1.89	1.344
S.11: Ratio of Pedanios 22/1®	1.89	1.344
S.12: Pharmacology of CBD	1.76	0.946
S.13: Safety profile of CBD use (e.g., contraindications, cautions, drug interactions)	1.89	0.959
S.14: Likelihood of dependence or addiction from CBD use	2.18	1.081
S.15: Effects of CBD on driving	2.23	1.100
S.16: Likelihood of withdrawal symptoms upon stopping use of CBD	2.15	1.132
S.17: Legal status of CBD in Malta	2.52	1.180
S.18: Legal status of CBD in other European countries	2.02	1.108

X^2 (17) = 278.74, $p < 0.001$

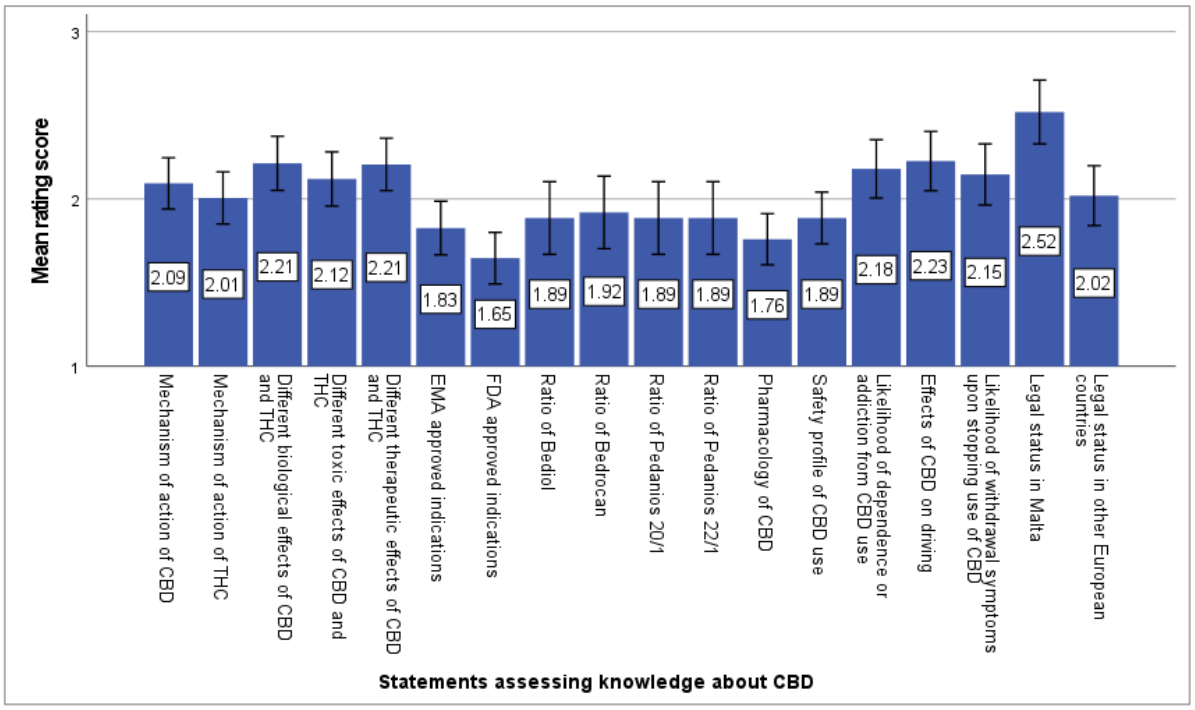

Figure 3.9 Error graph displaying the mean rating scores of the statements assessing knowledge about CBD (N=150)

The results of the Kruskal Wallis test between the provided statements and the categorical group being knowledge about CBD showed significant differences between the mean rating scores of nine statements since the p-value is less than the 0.05 level of significance (Table 3.23). The Kruskal Wallis test between the statements and gender, age, nationality, profession and years of practice did not show significant differences between the mean rating scores since the p-value exceeded the 0.05 level of significance.

Table 3.23 Kruskal Wallis test result between the provided statements and knowledge about CBD (N=150)

	Heard about CBD	Sample size	Mean	Std. Dev	P-value
S.1: Mechanism of action of CBD	Yes	146	2.12	0.946	0.012
	No	4	1.00	0.000	
S.3: Different biological effects of CBD and THC	Yes	146	2.24	0.999	0.036
	No	4	1.25	0.500	
S.5: Different therapeutic effects of CBD and THC	Yes	146	2.23	0.969	0.034
	No	4	1.25	0.500	
S.6: EMA approved indications	Yes	146	1.85	0.999	0.049
	No	4	1.00	0.000	
S.13: Safety profile of CBD use (e.g., contraindications, cautions, drug interactions)	Yes	146	1.91	0.961	0.037
	No	4	1.00	0.000	
S.14: Likelihood of dependence or addiction from CBD use	Yes	146	2.21	1.078	0.015
	No	4	1.00	0.000	
S.15: Effects of CBD on driving	Yes	146	2.26	1.096	0.012
	No	4	1.00	0.000	
S.16: Likelihood of withdrawal symptoms upon stopping use of CBD	Yes	146	2.18	1.131	0.021
	No	4	1.00	0.000	
S.17: Legal status in Malta	Yes	146	2.55	1.175	0.020
	No	4	1.25	0.500	

Table 3.24 demonstrates that healthcare professionals believe that CBD has an analgesic effect with 35% (n=53) and 23% (n=30) believing that the probability of this effect being produced is between 61-80% and 80-100%, respectively. Conversely, 49% (n=74) of the healthcare professionals believe that CBD does not produce a cardioprotective effect.

Table 3.24 Probability of therapeutic effect being caused by CBD according to healthcare professionals (N=150)

Therapeutic effect	**Probability of therapeutic effect**					
	0%	**1-20%**	**21-40%**	**41-60%**	**61-80%**	**80-100%**
Anxiolytic	8	16	32	34	45	15
Antipsychotic	34	39	35	26	15	1
Antitumour	58	44	21	14	13	0
Analgesic	5	9	24	29	53	30
Anti-inflammatory	15	33	25	38	28	11
Antiepileptic	22	29	33	22	26	18
Antiemetic	46	39	21	24	12	8
Antioxidant	73	38	16	14	6	3
Antidepressant	26	31	38	23	27	5
Cardioprotective	74	44	13	13	6	0
Neuroprotective	70	31	21	14	10	4

Figure 3.10 shows that out of the 35% (n=53) of healthcare professionals who believed that CBD has a 61-80% probability of producing an analgesic effect, 17% (n=25) were pharmacists.

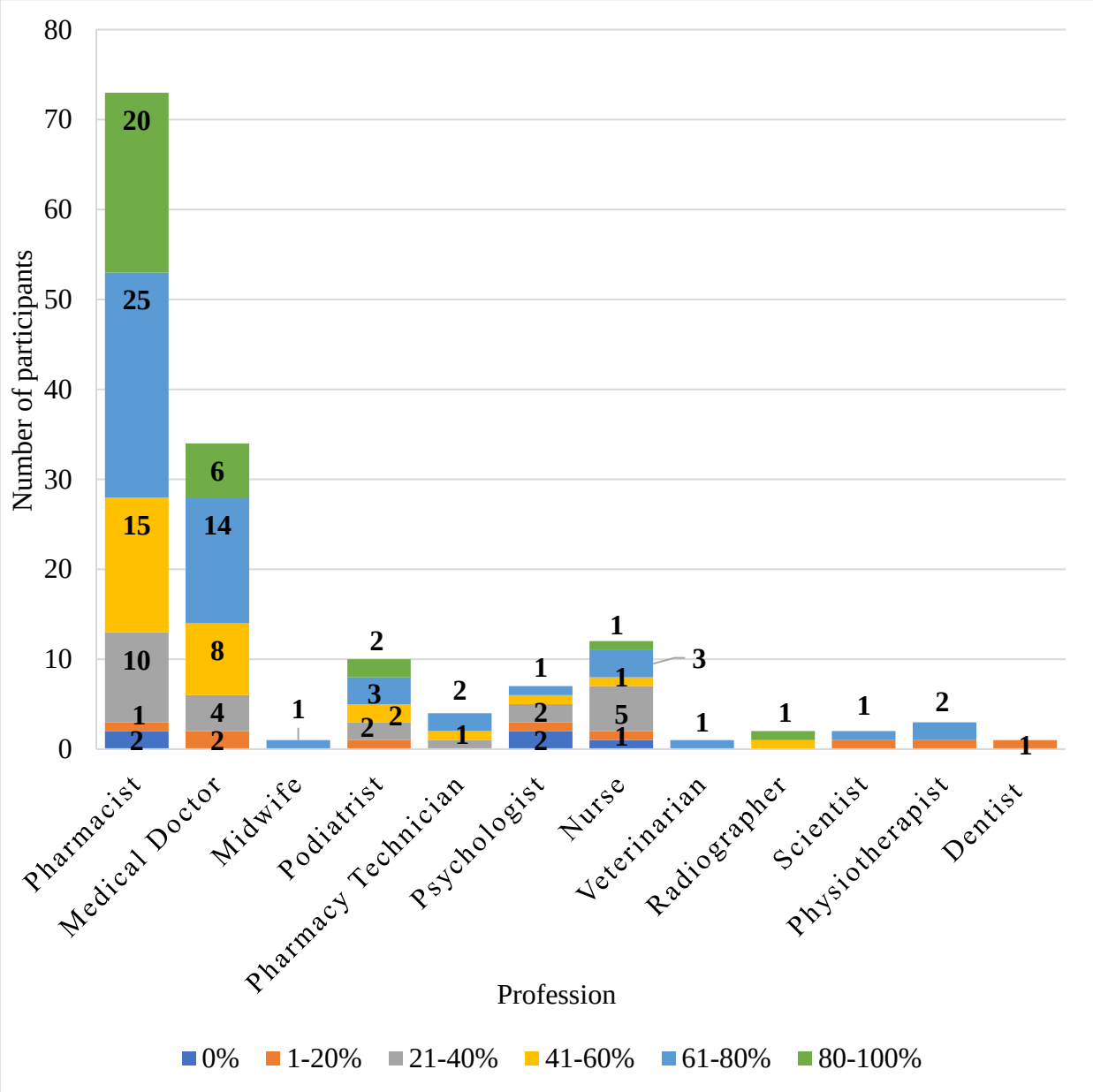

Figure 3.10 Probability of analgesic effect according to the different healthcare profession (N=150)

Six healthcare professionals believe that CBD has other additional therapeutic effects which consist of management of sleep disorders (n=2), appetite stimulant (n=1), negative and positive effects on fertility and decrease in insulin resistance (n=1), improvement in neurodevelopment disorders (n=1) and reduction in glaucoma (n=1).

With regards to side effects, results from Table 3.25 demonstrates that healthcare professionals (n=105) believe that sedation/somnolence are common to very common side effects caused by CBD followed by fatigue (n=79) and increased appetite (n=79). Fever (n=90) was believed to be a rare to very rare side effect of CBD followed by infections (n=80). Participants were able to not select any response if they believed that CBD does not cause any of the side effects, hence the total count not adding up to 150.

Eight participants believe that CBD has other additional side effects which are the following:

- Very common: incontinence when overdosing (n=1)
- Common: nausea (n=1)
- Uncommon: headache and mood changes (n=1)
- Uncommon: fertility problems (n=1)
- Frequency not mentioned: dependence (n=1)
- Frequency not mentioned: palpitations (n=1)
- Frequency not mentioned: dry mouth (n=1)
- Frequency not mentioned: delirium with the first few doses (n=1)

Table 3.25 Frequency of side effect being caused by CBD according to healthcare professionals (N=150)

Side effect	Frequency of side effect					
	Very common	Common	Uncommon	Rare	Very rare	Total
Aggression	5	32	67	21	19	144
Agitation	7	50	58	16	13	144
Abnormal behaviour	8	67	41	17	11	144
Cough	6	32	58	35	11	142
Decreased weight	10	34	60	31	9	144
Diarrhoea	15	53	51	19	7	145
Decreased appetite	17	39	51	27	12	146
Drooling	4	17	63	40	19	143
Fever	8	7	40	49	41	145
Fatigue	31	48	42	16	9	146
Infections	3	12	48	46	34	143
Irritability	11	53	48	22	10	144
Increased appetite	37	42	37	21	8	145
Liver disorders	9	19	57	40	19	144
Rash	11	22	55	37	18	143
Sedation, somnolence	44	61	27	9	7	148
Sleep disorders	23	52	40	19	9	143
Tremor	7	22	58	39	17	143
Vomiting	11	32	50	33	16	142

Results from Figure 3.11 demonstrate that 5% (n=8) of healthcare professionals think that vomiting and cough are not side effects caused by CBD. Only 1% (n=2) of the participants thought that CBD does not cause sedation and somnolence.

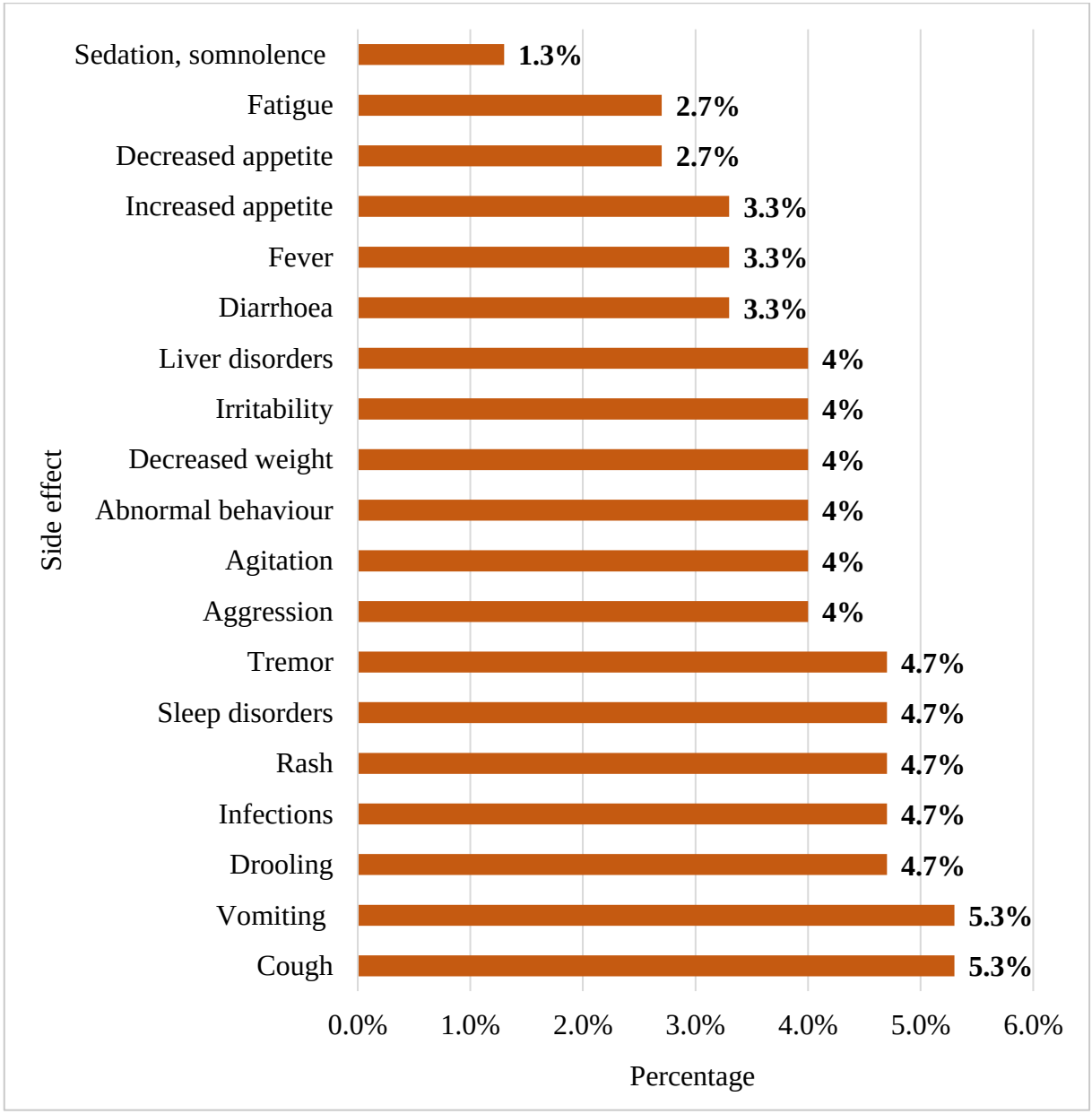

Figure 3.11 Number of healthcare professionals who think that CBD does not cause such side effect (N=150)

Results demonstrated that 75% of healthcare professionals (n=112) are not aware that there is only one FDA and EMA approved CBD-based product called Epidiolex® / Epidyolex®. Out of the 75% participants who answered 'No', 48% (n=54) were pharmacists while 22% (n=25) were medical doctors. Only 15% (n=22) of the participants were aware about Epidiolex® / Epidyolex®, out of which 50% (n=11) were pharmacists, 36% (n=8) were medical doctors and 9% (n=2) were podiatrists.

The Chi-square test was used to assess the association between the knowledge about Epidiolex® / Epidyolex® and profession. There was no statistical association since the p-value (0.515) exceeded the 0.05 level of significance.

To assess the knowledge of the participants regarding Epidiolex® / Epidyolex®, five 'True or False' questions were asked. The correct answers are all 'True'. Figure 3.12 reveals the answers of the healthcare professionals who are aware about Epidiolex® / Epidyolex®. The statement 'Dosing of Epidyolex® is weight dependent and the dose should be increased in weekly increments' was the only statement that received all 'True' answers.

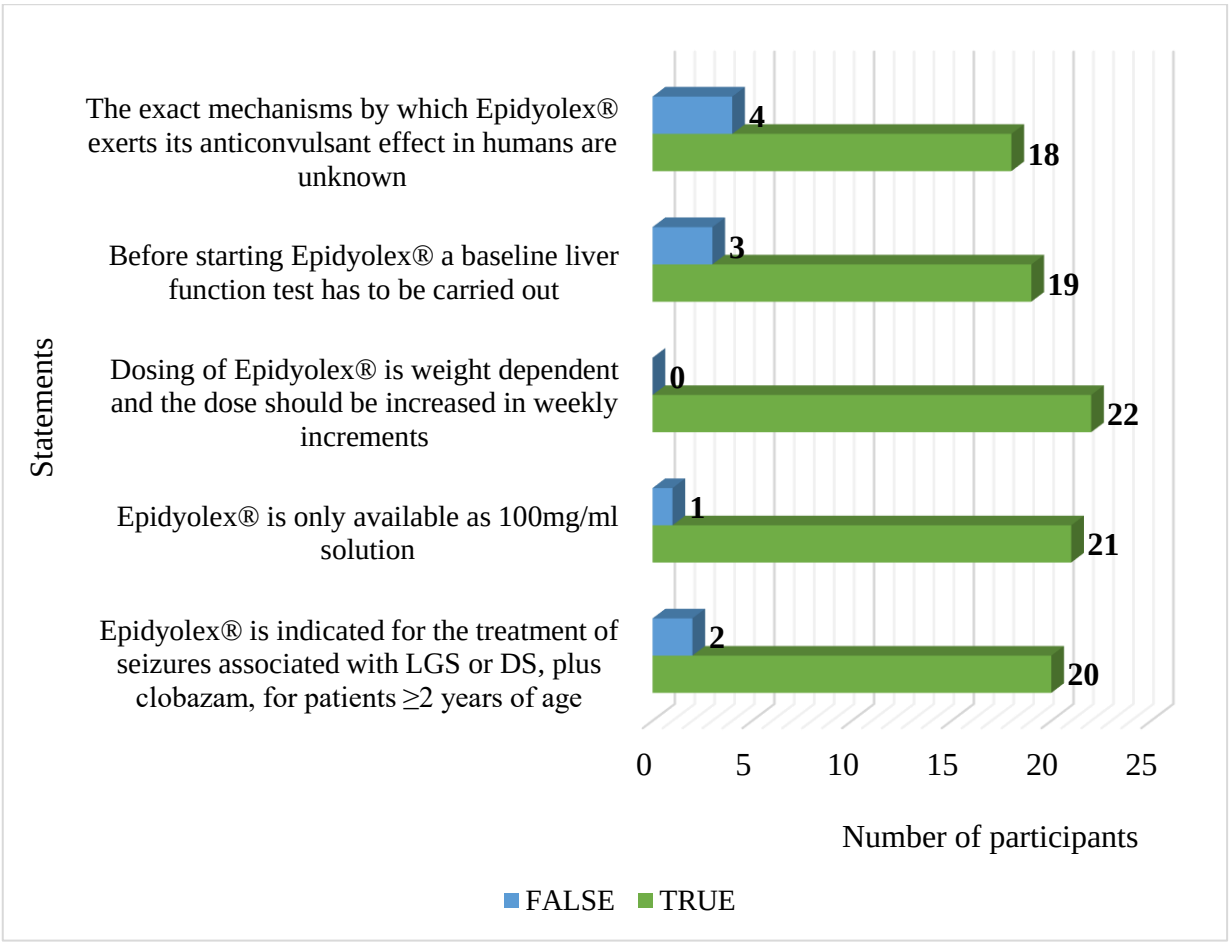

Figure 3.12 Statements assessing knowledge about Epidiolex® / Epidyolex® (n=22)

3.3.2 Perceptions of CBD

Sixty percent (n=90) of healthcare professionals believe that Epidyolex® should be available in Malta while only 5% (n=8) believe that it should not be available.

Results demonstrated that 53% (n=79) of the healthcare professionals believe that CBD products intended for medicinal use without a marketing authorization should not be legally available in Malta. Only 31% (n=46) of the healthcare professionals believe that they should be available.

If CBD products were to be legally available in Malta, 67% (n=101) of the healthcare professionals believe that they should be classified as POM, while 7% (n=10) believe that CBD products should be classified as general sales meaning that they can be bought from retail shops. Sixty-seven healthcare professionals think that if CBD products were to be legally available in Malta and were to be classified as POM, they should be prescribed without the need for a ‘green’ prescription and control card (Figure 3.13).

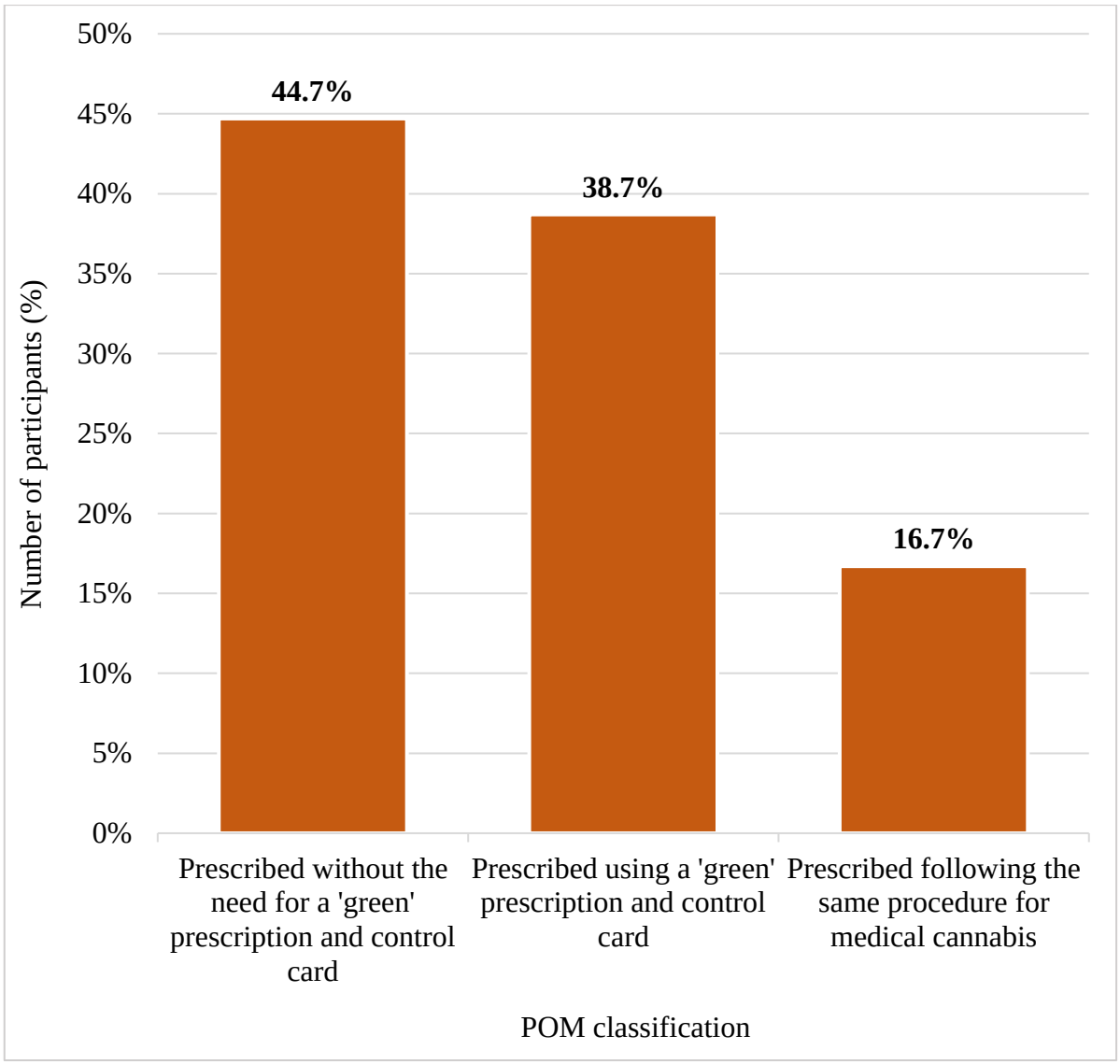

Figure 3.13 POM classification of CBD products (N=150)

Results displayed in Table 3.26 demonstrate that a larger percentage of healthcare professionals who believe that Epidyolex® should be available in Malta (86.4%) were aware about Epidyolex® compared to those participants (55.4% and 56.3%) who were not or were not sure if they were aware about Epidyolex®. These percentage differences are significant since the p-value (0.032) is less than the 0.05 level of significance.

Table 3.26 Chi-square test between awareness about Epidyolex® and if it should be accessible in Malta (N=150)

			Are you aware that there is only one FDA and EMA approved, CBD-based product called Epidiolex® / Epidyolex®?		
			Yes	**No**	**Not sure**
Do you think Epidyolex® should be available in Malta?	**Yes**	Percentage	86.4%	55.4%	56.3%
	No	Percentage	9.1%	4.5%	6.3%
	Not sure	Percentage	4.5%	40.2%	37.5%

X^2 (4) = 10.53, p = 0.032

Table 3.27 demonstrates that a larger percentage of healthcare professionals who believe or are not sure that Epidyolex® should be available in Malta (68.1% and 29.8%) believe that CBD products intended for medicinal use, without a marketing authorisation, should also be legally available in Malta. These percentage differences are significant since the p-value (0.020) is less than the 0.05 level of significance.

The results of the Chi-square test performed to assess the association between Epidyolex® being available in Malta and gender (p = 0.213), age (p = 0.101), profession (p = 0.420), years of practice (p = 0.272), knowledge about CBD (p = 0.225) and whether a patient had asked about CBD (p = 0.114) resulted in no statistical association as the p-values exceeded the 0.05 level of significance.

Table 3.27 Chi-square test between availability of Epidyolex® and CBD products in Malta (N=150)

			Do you think that CBD products intended for medicinal use, without a marketing authorisation, should be legally available in Malta?		
			Yes	**No**	**Not sure**
Do you think Epidyolex should be available in Malta?	**Yes**	Percentage	68.1%	63.3%	33.3%
	No	Percentage	2.1%	7.6%	4.2%
	Not sure	Percentage	29.8%	29.1%	62.5%

X^2 (4) = 11.61, p = 0.020

Table 3.28 and Table 3.29 show that healthcare professionals aged between 18-25 (54.5%) and who have been practicing their profession for 1-5 years (40.6%) believe that CBD products intended for medicinal use, without a marketing authorisation, should be legally available in Malta. These percentage differences are significant since the p-values are less than the 0.05 level of significance.

Table 3.28 Chi-square test between availability of CBD products in Malta and age (N=150)

			Age			
			18-25	**26-40**	**41-60**	**60+**
Do you think that CBD products intended for medicinal use, without a marketing authorisation, should be legally available in Malta?	**Yes**	Percentage	54.5%	24.1%	31.3%	0.0%
	No	Percentage	33.3%	58.2%	53.1%	83.3%
	Not sure	Percentage	12.1%	17.7%	15.6%	16.7%

X^2 (6) = 13.23, p = 0.040

Table 3.29 Chi-square test between availability of CBD products in Malta and years of practice (N=150)

			Years of practice				
			1-5	**6-10**	**11-20**	**21-30**	**>30**
Do you think that CBD products intended for medicinal use, without a marketing authorisation, should be legally available in Malta?	**Yes**	Percentage	40.6%	31.0 %	21.7%	29.4%	11.8%
	No	Percentage	35.9%	62.1 %	69.6%	52.9%	76.5%
	Not sure	Percentage	23.4%	6.9%	8.7%	17.6%	11.8%

X^2 (8) = 16.20, p = 0.040

Table 3.30 demonstrates that a larger percentage of participants who believe that CBD products should be classified as OTC (55.3%) believe that CBD products intended for medicinal use, without a marketing authorisation, should be legally available in Malta. These percentage differences are significant since the p-value (<0.001) is less than the 0.05 level of significance.

The results of the Chi-square test performed to assess the association between CBD products being legally available in Malta and gender (p = 0.914), profession (p = 0.053) and knowledge about CBD (p = 0.119) resulted in no statistical association as the p-values exceeded the 0.05 level of significance.

Table 3.30 Chi-square test between availability of CBD products in Malta and their classification (N=150)

			If CBD products were to be legally available in Malta, which category do you think they should be classified in?		
			POM	**OTC**	**General sales**
Do you think that CBD products intended for medicinal use, without a marketing authorisation, should be legally available in Malta?	**Yes**	Percentage	20.8%	55.3%	45.5%
	No	Percentage	64.4%	28.9%	27.3%
	Not sure	Percentage	14.9%	15.8%	27.3%

X^2 (4) = 20.21, p <0.001

Table 3.31 demonstrates that there is a larger percentage of healthcare professionals who have been practicing their profession between 6-10 years (31.0%) who believe that CBD products should be classified as OTC and there is a larger percentage of healthcare professionals who have been practicing their profession for 1-5 years (15.6%) who believe that CBD products should be classified as general sales. These percentage differences are significant since the p-value (0.008) is less than the 0.05 level of significance. The results of the Chi-square test performed to assess the association between classification of CBD products and gender (p = 0.935), age (p = 0.231), profession (p = 0.478), knowledge about CBD (p = 0.369), whether a patient asked about CBD (p = 0.511) resulted in no statistical association as the p-values exceeded the 0.05 level of significance.

Table 3.31 Chi-square test between classification of CBD products and years of practice (N=150)

			Years of practice				
			1-5	**6-10**	**11-20**	**21-30**	**>30**
If CBD products were to be legally available in Malta, which category do you think they should be classified in?	**POM**	Percentage	54.7 %	69.0 %	73.9%	100.0 %	70.6 %
	OTC	Percentage	29.7 %	31.0 %	26.1%	0.0%	23.5 %
	General sales	Percentage	15.6 %	0.0%	0.0%	0.0%	5.9%

X^2 (8) = 20.69, p = 0.008

The results of the Chi-square test performed to assess the association between POM classification of CBD products and gender ($p = 0.301$), age ($p = 0.264$), profession ($p = 0.218$), years of practice ($p = 0.423$), knowledge about CBD ($p = 0.718$), whether a patient asked about CBD ($p = 0.692$) resulted in no statistical association as the p-values exceeded the 0.05 level of significance.

As observed from Table 3.32, 69% (n=104) of healthcare professionals would feel comfortable in prescribing or recommending CBD in painful conditions followed by 50% of healthcare professionals (n=75) stating that they would prescribe or recommend CBD for insomnia. Schizophrenia was the condition in which 63% (n=95) of the healthcare professionals would not feel comfortable in prescribing or recommending CBD.

Table 3.32 Healthcare professionals' level of comfort in prescribing or recommending CBD in various medical conditions (N=150)

Condition		**Would you feel comfortable prescribing or recommending CBD in?**		
		Yes	**No**	**Maybe**
Anxiety	Percentage	44.7%	24.7%	30.6%
Arthritis	Percentage	42%	28.7%	29.3%
Alzheimer's Disease	Percentage	20%	54%	26%
Autism	Percentage	16.7%	57.3%	26%
Cancer	Percentage	45.3%	29.3%	25.3%
Depression	Percentage	36%	28.7%	35.3%
Epilepsy	Percentage	37.3%	35.3%	27.3%
Hypertension	Percentage	10%	57.3%	32.7%
Inflammation	Percentage	35.3%	34%	30.7%
Insomnia	Percentage	50%	25.3%	24.7%
Migraine	Percentage	41.3%	29.3%	29.3%
Multiple Sclerosis	Percentage	36.7%	32%	31.3%
Nausea and vomiting	Percentage	26.7%	47.3%	26%
Pain	Percentage	69.3%	16%	14.7%
Parkinson's Disease	Percentage	32.7%	43.3%	24%
Post-Traumatic Stress Disorder	Percentage	38%	38%	24%
Schizophrenia	Percentage	16%	63.3%	20.7%
Skin conditions e.g., eczema, psoriasis	Percentage	26.7%	51.3%	22%

Figure 3.14 reveals 33% (n=50) of the healthcare professionals who would feel comfortable in prescribing or recommending CBD for painful conditions were pharmacists, followed by medical doctors (n=25) and nurses (n=10).

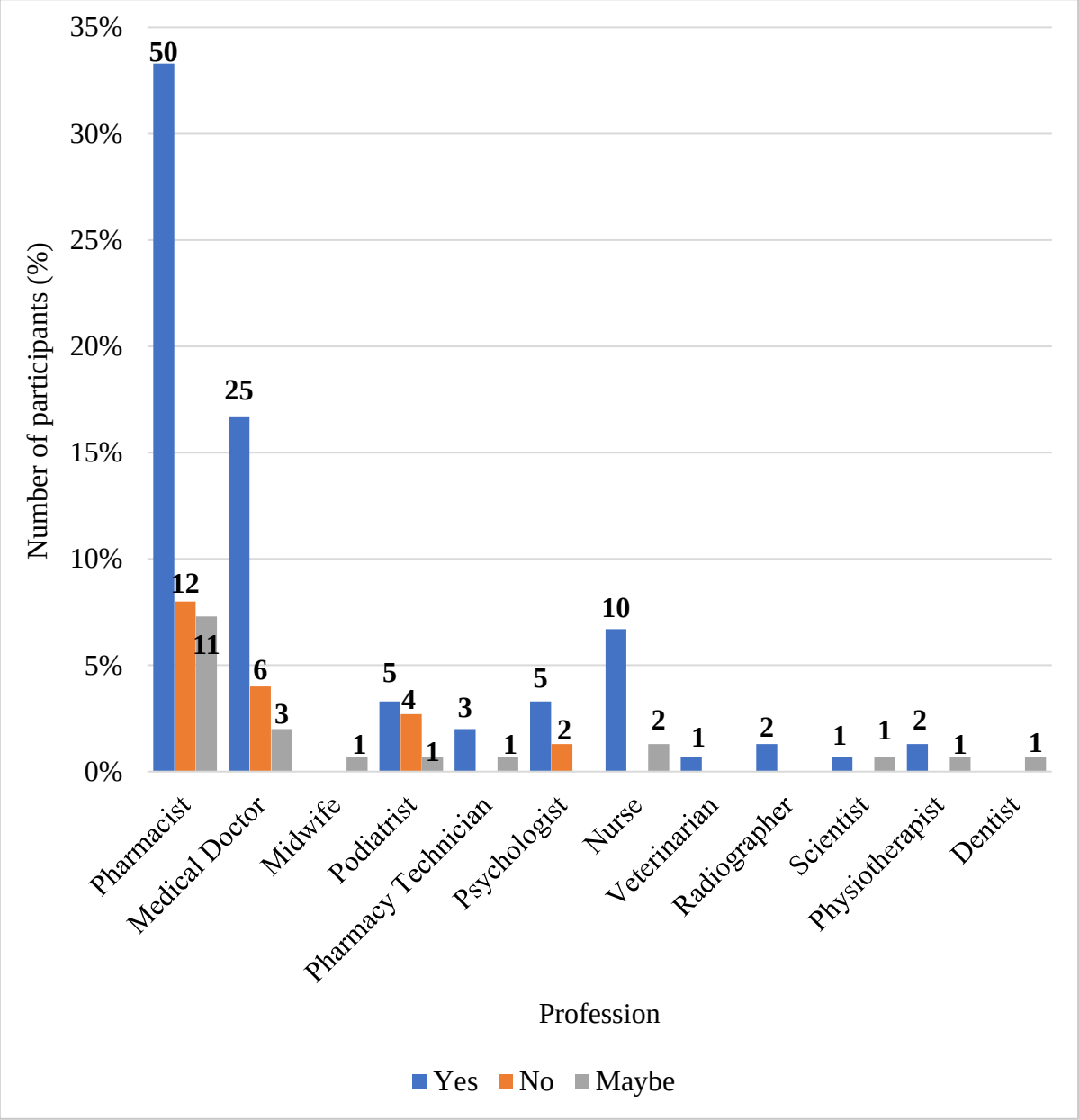

Figure 3.14 Different healthcare professions stating their level of comfort in prescribing or recommending CBD in painful conditions (N=150)

Table 3.33 demonstrates that the largest mean rating score is 4.41 of S.1 indicating the highest agreement out of all the provided statements. The mean rating scores provided to the statements vary significantly since the p-value (approx. 0) is less than the 0.05 criterion.

The error bar graph in Figure 3.15 indicates that the mean rating scores differ significantly since slight overlapping of confidence intervals is observed.

Table 3.33 Statements assessing the perception of healthcare professionals about CBD

Statements	Mean	Std. Deviation
S.1: There is a lack of education among the general public about CBD and its use in medical conditions	4.41	0.812
S.2: There is not enough data about the side effects of CBD products	3.31	1.081
S.3: CBD products for medicinal use should be available for prescribing or recommending	3.99	0.969
S.4: CBD products should only be legally available in pharmacies	4.17	1.048
S.5: CBD products should be legally available in health shops, grocery shops and other retail shops	1.84	1.087
S.6: CBD products should not be prescribed or recommended due to potential impairing effects on driving	2.37	1.007
S.7: CBD products should be prescribed or recommended for minor ailments (e.g., headache, joint pain, minor sleep disorders) in preference to conventional medicine	2.57	1.138
S.8: CBD is very safe and has minimal side effects since it is a naturally occurring compound derived from cannabis	2.89	1.150
S.9: CBD products intended for medicinal use should only be considered if there is no viable alternative medicine	2.99	1.187
S.10: CBD products should be available on prescription only, to avoid misuse and abuse of such products	3.66	1.345
S.11: CBD should be classified as a dangerous or harmful drug	2.59	1.265
S.12: There are misconceptions among general public about CBD use	4.00	0.941
S.13: Healthcare professionals are concerned about a patient's perception of a healthcare professional prescribing or recommending CBD for medicinal use	3.38	1.008
S.14: CBD use will lead to the use of more dangerous drugs (e.g., cocaine, heroin)	2.27	1.053
S.15: CBD for medicinal use should be manufactured only in appropriately licensed EU GMP certified facilities	4.31	0.962
S.16: The quality between CBD products used for recreational purposes and for medicinal use should be the same	3.24	1.422
S.17: CBD products used for recreational purposes should be decriminalised	3.17	1.308

X^2 (16) = 863.49, $p < 0.001$

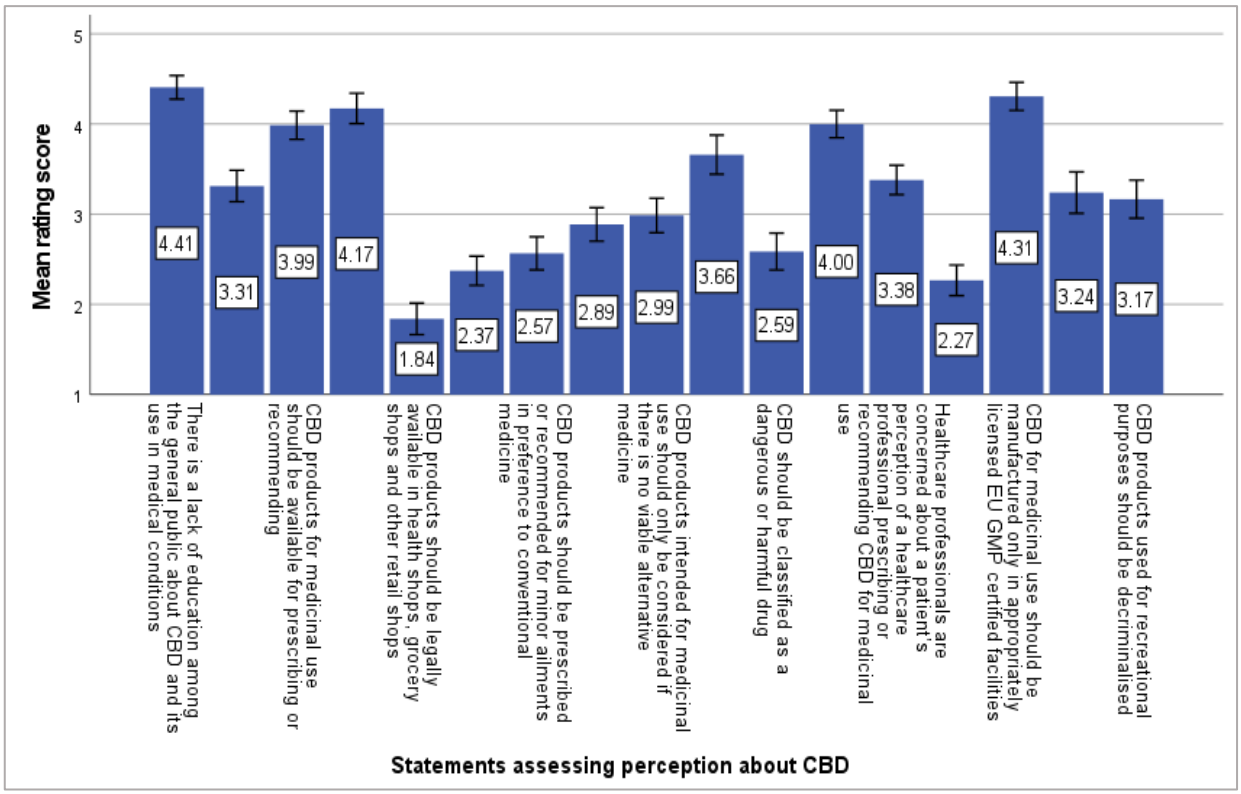

Figure 3.15 Error graph displaying the mean rating scores of the statements assessing perception about CBD (N=150)

The results of the Kruskal Wallis test between the provided statements and gender, age, nationality, profession and years of practice did not show significant differences between the mean rating scores since the p-values exceeded the 0.05 level of significance. The results of the Kruskal Wallis test between the provided statements and knowledge about CBD showed significant differences between the mean rating scores of the statements 1, 3, 12 and 15 since the p-value is less than the 0.05 level of significance. The results of the Kruskal Wallis test between the provided statements and whether a patient asked about CBD before showed significant differences between the mean rating scores of the statements 1, 12, 13 and 15 since the p-value is less than the 0.05 level of significance.

The results of the Kruskal Wallis test between the provided statements and availability of CBD products in Malta (Table 3.34) showed significant differences between the mean rating scores of all the statements except for statements 1 (p-value = 0.364), 2 (p-value = 0.323), 12 (p-value = 0.588), 13 (p-value = 0.305) and 15 (p-value = 0.864).

Table 3.34 Kruskal Wallis test result between the provided statements and availability of CBD products in Malta (N=150)

	CBD product available in Malta	**Sample size**	**Mean**	**Std. Dev**	**P-value**
S.3: CBD products for medicinal use should be available for prescribing or recommending	Yes	47	4.43	0.683	<0.001
	No	79	3.80	1.055	
	Not sure	24	3.75	0.897	
S.4: CBD products should only be legally available in pharmacies	Yes	47	3.96	1.179	0.004
	No	79	4.42	0.871	
	Not sure	24	3.79	1.141	
S.5: CBD products should be legally available in health shops, grocery shops and other retail shops	Yes	47	2.15	1.251	<0.001
	No	79	1.52	0.845	
	Not sure	24	2.29	1.160	
S.6: CBD products should not be prescribed or recommended due to potential impairing effects on driving	Yes	47	1.98	0.821	0.005
	No	79	2.61	1.043	
	Not sure	24	2.38	1.013	
S.7: CBD products should be prescribed or recommended for minor ailments (e.g., headache, joint pain, minor sleep disorders) in preference to conventional medicine	Yes	47	2.89	1.220	0.002
	No	79	2.27	1.083	
	Not sure	24	2.92	0.881	

Table 3.34 Kruskal Wallis test result between the provided statements and availability of CBD products in Malta (N=150)

S.8: CBD is very safe and has minimal side effects since it is a naturally occurring compound derived from cannabis	Yes	47	3.43	1.016	<0.001
	No	79	2.43	1.082	
	Not sure	24	3.33	1.007	
S.9: CBD products intended for medicinal use should only be considered if there is no viable alternative medicine	Yes	47	2.49	1.177	<0.001
	No	79	3.34	1.153	
	Not sure	24	2.79	0.932	
S.10: CBD products should be available on prescription only, to avoid misuse and abuse of such products	Yes	47	3.00	1.474	<0.001
	No	79	4.05	1.120	
	Not sure	24	3.67	1.308	
S.11: CBD should be classified as a dangerous or harmful drug	Yes	47	1.85	1.179	<0.001
	No	79	3.03	1.143	
	Not sure	24	2.58	1.176	
S.14: CBD use will lead to the use of more dangerous drugs (e.g., cocaine, heroin)	Yes	47	1.77	0.983	<0.001
	No	79	2.46	0.997	
	Not sure	24	2.63	1.056	
S.16: The quality between CBD products used for recreational purposes and for medicinal use should be the same	Yes	47	3.64	1.276	0.008
	No	79	2.90	1.429	
	Not sure	24	3.58	1.442	
S.17: CBD products used for recreational purposes should be decriminalised	Yes	47	3.74	1.310	<0.001
	No	79	2.76	1.222	
	Not sure	24	3.38	1.135	

The results of the Kruskal Wallis test between the provided statements and classification of CBD products (Table 3.35) showed significant differences between the mean rating scores of all the statements except for statements 1 (p-value = 0.796), 2 (p-value = 0.307), 6 (p-value = 0.722) and 12 (p-value = 0.127).

Table 3.3*5* Kruskal Wallis test result between the provided statements and classification of CBD products in Malta (N=150)

	Classification	Sample size	Mean	Std. Dev	P-value
S.3: CBD products for medicinal use should be available for prescribing or recommending	POM	101	3.77	0.979	<0.001
	OTC	38	4.45	0.795	
	General sales	11	4.36	0.809	
S.4: CBD products should only be legally available in pharmacies	POM	101	4.42	0.725	<0.001
	OTC	38	4.18	1.087	
	General sales	11	1.91	0.701	
S.5: CBD products should be legally available in health shops, grocery shops and other retail shops	POM	101	1.57	0.829	<0.001
	OTC	38	1.87	0.906	
	General sales	11	4.18	0.982	
S.7: CBD products should be prescribed or recommended for minor ailments (e.g., headache, joint pain, minor sleep disorders) in preference to conventional medicine	POM	101	2.36	1.154	<0.001
	OTC	38	2.89	0.953	
	General sales	11	3.36	1.027	
S.8: CBD is very safe and has minimal side effects since it is a naturally occurring compound derived from cannabis	POM	101	2.68	1.067	<0.001
	OTC	38	3.13	1.234	
	General sales	11	3.91	0.944	
S.9: CBD products intended for medicinal use should only be considered if there is no viable alternative medicine	POM	101	3.28	1.124	<0.001
	OTC	38	2.45	1.155	
	General sales	11	2.18	0.874	
S.10: CBD products should be available on prescription only, to avoid misuse and abuse of such products	POM	101	4.23	0.968	<0.001
	OTC	38	2.71	1.293	
	General sales	11	1.73	0.786	
S.11: CBD should be classified as a dangerous or harmful drug	POM	101	2.98	1.149	<0.001
	OTC	38	1.89	1.181	
	General sales	11	1.36	0.674	
S.13: Healthcare professionals are concerned about a patient's perception of a healthcare professional prescribing or recommending CBD for medicinal use	POM	101	3.39	0.959	0.027
	OTC	38	3.55	1.132	
	General sales	11	2.73	0.786	

Table 3.35 Kruskal Wallis test result between the provided statements and classification of CBD products in Malta (N=150)

S.14: CBD use will lead to the use of more dangerous drugs (e.g., cocaine, heroin)	POM	101	2.52	1.006	<0.001
	OTC	38	1.71	0.956	
	General sales	11	1.82	0.982	
S.15: CBD for medicinal use should be manufactured only in appropriately licensed EU GMP certified facilities	POM	101	4.23	0.979	0.014
	OTC	38	4.63	0.786	
	General sales	11	3.91	1.136	
S.16: The quality between CBD products used for recreational purposes and for medicinal use should be the same	POM	101	2.90	1.382	<0.001
	OTC	38	3.97	1.219	
	General sales	11	3.82	1.401	
S.17: CBD products used for recreational purposes should be decriminalised	POM	101	2.80	1.217	<0.001
	OTC	38	3.84	1.128	
	General sales	11	4.18	1.328	

Figure 3.16 demonstrates that 45% of healthcare professionals (n=67) agree to strongly agree that CBD products used for recreational purposes should be decriminalised.

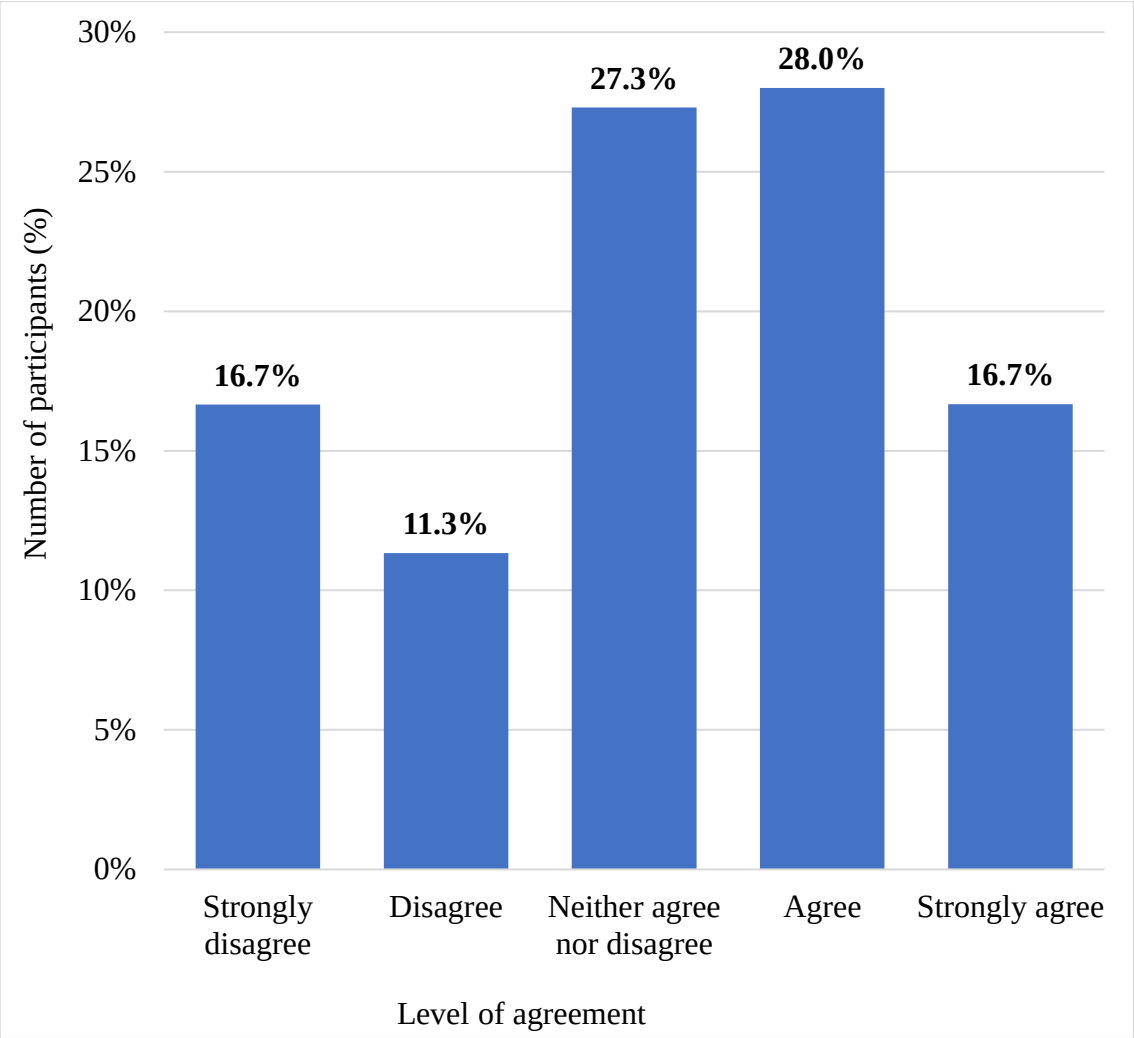

Figure 3.16 CBD products used for recreational purposes should be decriminalised (N=150)

3.3.3 Barriers related to CBD

Figure 3.17 demonstrates that 65% (n=97) of healthcare professionals (out of which 50 were pharmacists) believe that if CBD were to be legally available in Malta, personal beliefs of healthcare professionals would pose as the highest potential barrier. Individuals were able to select multiple responses, hence the bar chart adding up to over 100%.

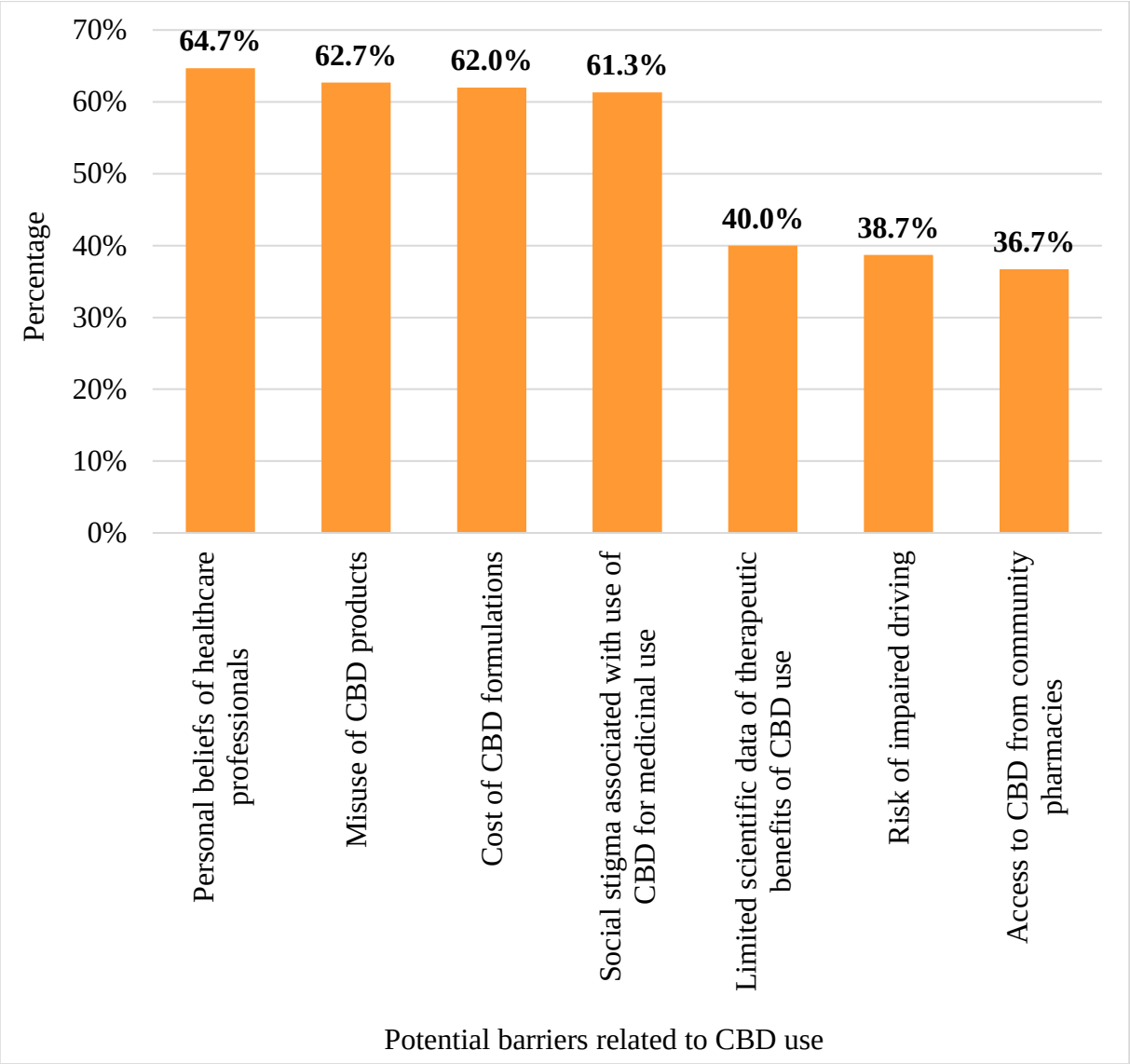

Figure 3.17 Potential barriers related to CBD use (N=150)

The Chi-square test was used to assess the association between the potential barriers related to CBD use and categorical variables. The results of the Chi-square test performed to assess the association between potential barriers related to CBD use and gender ($p = 0.979$), age ($p = 1.000$), profession ($p = 1.000$), years of practice ($p = 0.999$), knowledge of CBD ($p = 0.964$), whether a patient asked about CBD ($p = 0.740$) and whether CBD products should be available in Malta ($p = 0.523$) resulted in no statistical association as the p-values exceeded the 0.05 level of significance.

CHAPTER 4

DISCUSSION

4.1 Evaluation of the results generated from the systematic literature search

The purpose of the systematic literature search was to compare research related to potential therapeutic benefits of CBD in order to fulfil the aim of investigating the science and realities related to CBD. The systematic literature search resulted into 126 articles, where the majority (n=55) were animal studies**.** This indicates the need for further human studies and further research about the effects of CBD (Jones and Vlachou, 2020; Rapin et al., 2021).

The results gathered from the systematic search indicate that as suggested by other studies; Russo, (2017); Lucas et al., (2018); Huestis et al., (2019); Kis et al., (2019); Britch et al., (2020); García-Gutiérrez et al., (2020); Kicman and Toczek, (2020) and Mlost et al., (2020). CBD reported to have potential analgesic effects, anti-inflammatory activity, anxiolytic effects and anticonvulsant effects. The results demonstrate that CBD has over sixty recognised targets and has a diverse and multifaceted mechanism of action (Britch et al., 2020; García-Gutiérrez et al., 2020; Mlost et al., 2020; Kicman and Toczek, 2020).

Studies demonstrated that CBD produced an anti-inflammatory effect via different pathways such as decrease of pro-inflammatory cytokines, stimulation of transcription factors and reduction of other inflammatory cells. A study conducted by Karmaus et al., (2012) showed that CBD increased the levels of inflammatory cells and monocytes. There was contradictory data with regards to the anti-oxidant effect since CBD demonstrated to produce and anti-oxidant effect by decreasing ROS levels however a study by Singer et al., (2015) showed that CBD increased ROS levels instead and Jarocka-Karpowicz et al., (2020) demonstrated that CBD increased oxidation and inflammation. CBD reported anti-tumour, antiangiogenic and apoptotic effects but also reported inhibition of apoptosis or

no apoptotic effect at all (Solinas et al., 2012; Gigli et al., 2017). CBD produced a reduction in myocardial dysfunction, cardiac fibrosis, inflammation and myocardial cell death. CBD also had an effect on HR, SBP and DBP. These results support the findings of the study conducted by Kicman and Toczek, (2020).

The majority of the studies (n=33) demonstrated that CBD had an effect on mental health disorders. Results demonstrate that CBD increased levels or partially restored levels of serotonin (Avraham et al., 2011; Peres et al., 2018). These findings support the data that one of the targets of CBD are serotonin receptors (Russo, 2017; Brown and Winterstein, 2019; Baswan et al., 2020; Britch et al., 2020; García-Gutiérrez et al., 2020). Although there were more studies which demonstrated that CBD had an effect on mental health disorders, the average impact factor was that of 5.31. The journals consisting of the studies which demonstrated that CBD has an effect on neurological conditions had the highest impact factor being 14.39. A high impact factor indicates that the journals in which the studies were published in are of high importance and influence.

4.2 Evaluation of results generated from the general public questionnaire

The purpose of the questionnaire for the general public was to assess the knowledge and perception of the general public about CBD in order to fulfil the aim of investigating the myths and realities related to CBD.

4.2.1 Knowledge about CBD

Results demonstrate that the majority of the participants (n=361) had heard about CBD prior to this questionnaire, social media/news being the main source of information. The general public is knowledgeable that CBD is available in several formulations and that CBD and THC produce different biological effects. This indicates that the general public is knowledgeable about the difference between CBD and THC. Participants aged between 26-40 years are most aware that CBD might not cause a euphoric or 'high' sensation. Euphoric or 'high' sensation is associated with THC (Lachenmeier et al., 2020). The Kruskal Wallis test indicates that participants aged between 18-25 years are more knowledgeable about CBD than other age groups. Results indicated that participants who were aware about CBD, were more knowledgeable about CBD.

The results indicate that participants did not believe the misconception that in humans CBD is converted to THC. According to the study by Crippa et al., (2020), THC was not detected after oral administration of CBD.

There was a significant difference with regards to nationality and the statements assessing knowledge about CBD. Non-Maltese participants demonstrated to be more knowledgeable about CBD than Maltese participants especially in the statements stating that CBD and THC are naturally occurring compounds derived from cannabis and

produce different biological effects and that CBD is available in several formulations. This could be due to CBD products being newly available in Malta.

Although the anti-epileptic effect of CBD resulted in the approval of only one CBD-based medicinal product called Epidiolex® (USA name) / Epidyolex® (European name) which is indicated for the treatment of drug-resistant epilepsies, only 45% (n=180) of the participants believe that CBD has an anti-epileptic effect. The majority of the participants (n=314) believe that CBD has an analgesic effect, yet there is no FDA nor EMA approved CBD medicinal product indicated for painful conditions.

Results demonstrate that the majority of the participants who believe that CBD has a therapeutic effect were female, aged between 26-40 years and had a tertiary level of education. Findings demonstrate there were participants that believed or did not know if CBD has any therapeutic effects. In the study conducted by Lovecchio et al., (2021), participants who were using CBD reported that CBD had no therapeutic effects. With regards to the knowledge of side effects caused by CBD, participants were asked to tick which side effects they thought that CBD caused. Results demonstrated that the majority of the general public (n=180) believe that CBD causes sedation and somnolence however 8% (n=32) believe that CBD does not have any side effects and 3.8% (n=15) of the participants do not know if CBD has any side effects. The results gathered from this study support the findings of the study conducted by Huestis et al., (2019) where sedation was reported to be one of the most frequent side effects experienced by participants. The Chi-square demonstrated that 8.3% (n=30) of the participants who are knowledgeable about CBD, believe that CBD does not cause side effects. This indicates a lack of knowledge since the side effects mentioned in the questionnaire were all common to very common side effects caused by Epidiolex® / Epidyolex® (Huestis et al., 2019).

4.2.2 Perceptions and barriers of CBD

The results indicate that the majority of the general public (n=342) believe that CBD products intended for medicinal use should be available in Malta yet participants aged between 60 years and over believe that CBD products intended for medicinal use should not or are unsure if they should be available in Malta. Participants believe that if CBD products were to be legally available in Malta, they should be classified as POM. These results are in agreement with the findings from the study conducted by Leszko and Meenrajan, (2021) where participants suggested that CBD products should not be OTC. Still, there were individuals (n=84) who believe that CBD should be classified as general sales meaning that CBD products may be bought from retail shops such as health shops. Participants who believe that CBD should be available in Malta perceive that CBD products available in health shops and pharmacies are of the same quality, safety and efficacy. This might be a misconception as two studies, one conducted by Bonn-Miller et al., (2017) and the other carried out by Mazzetti et al., (2021) demonstrated that some CBD products analysed had different CBD or THC concentrations than the stated concentrations.

Participants agreed that healthcare professionals should be able to recommend or prescribe CBD products having the majority of participants believing that CBD products recommended or prescribed by a healthcare professional (e.g., pharmacist, physician, nurse) are more likely to be used by patients. In agreement with the study conducted by Schilling et al., (2021), participants disagreed that CBD is a dangerous or harmful drug. Participants believe that CBD use will not lead to the use of more dangerous drugs such as cocaine and heroin however participants aged 60 years and over tended to agree more than other age groups that CBD is a gateway drug. Participants that had never heard about CBD before and who do not believe that CBD products should be available in Malta,

believe that CBD use can lead to the use of more dangerous drugs (e.g., cocaine, heroin) and that CBD products used for recreational purposes should be not be decriminalised. Findings indicate that participants who had heard about CBD before believe that CBD does not cause potential impairing effect on driving. These results are in disagreement with the study carried out by Wershoven et al., (2020) where patients had a concern that CBD might have potential effects on driving.

The participants who believe that CBD should be available in Malta, believe that CBD products should be used in preference to conventional medicine and that CBD products should be used for minor and major ailments. Individuals from the studies conducted by Berg et al., (2020) and Lovecchio et al., (2021) found CBD to be beneficial in the management of pain, insomnia and anxiety among other conditions.

Participants identified social stigma associated with the use of CBD as the highest potential barrier. In addition, members of the general public (n=210) have the perception that the potential use of CBD might cause judgement or conflicts between health care professionals and patients. This was also a concern expressed by individuals participating in the study conducted by Hua et al., (2021) and in another study conducted by Leszko and Meenrajan (2021).

4.3 Evaluation of results generated from the healthcare professional questionnaire

The objective of the questionnaire for healthcare professionals was to assess the knowledge and perception of healthcare professionals about CBD in order to fulfil the aim of investigating the myths and realities related to CBD.

4.3.1 Knowledge about CBD

Results demonstrate that the majority of the healthcare professionals (n=146) had heard about CBD prior to this questionnaire, with social media/news being the main source of information. Results demonstrate that the majority of healthcare professionals, especially pharmacists, had patients asking them about CBD and its use. This study demonstrates that healthcare professionals are somewhat to not knowledgeable about CBD. These results are in accordance with a study conducted by Link et al., (2020), which showed that pharmacists lacked knowledge about OTC CBD products and felt unprepared or incompetent in advising patients about CBD products. One patient concern reported by Wershoven et al., (2020) was the limited scientific data about CBD to help guide healthcare professionals about CBD. Results indicated that healthcare professionals are not knowledgeable about the THC:CBD ratios of Bediol®, Bedrocan®, Pedanios 20/1® and Pedanios 22/1® which are available in Malta. This indicates the need for improved training about MC. Similar findings are observed in the study conducted by Karanges et al., (2018) in which healthcare professionals believed that their knowledge regarding MC was inadequate and concluded that training on MC needs to be improved.

The majority (n=145) of the healthcare professionals claim that CBD produces an analgesic effect, where the probability of this effect being produced is believed to be between 41-100%. Although there is no FDA nor EMA approved CBD product for the

management of pain, a study carried out by Schilling et al., (2021) demonstrated that participants who were using CBD found it effective in reducing their pain and in weaning pain medications. Healthcare professionals (n=128) believe that CBD has an antiepileptic activity. With regards to the knowledge of side effects caused by CBD, healthcare professionals were also asked to tick which side effects they thought that CBD caused and its frequency. Sedation and somnolence were believed to be common to very common side effects caused by CBD. Drooling, fever and infections were believed to be rare to very rare side effects of CBD. These results indicate different levels of knowledge among healthcare professionals because the side effects mentioned in the questionnaire were all common to very common side effects caused by Epidiolex® / Epidyolex® (Huestis et al., 2019). Epidiolex® / Epidyolex® is the only FDA and EMA approved CBD-based product (Corroon and Phillips, 2018; Brunetti et al., 2020). Results displayed that the majority of healthcare professionals (n=112) are not aware about Epidiolex® / Epidyolex®, however those healthcare professionals (n=22) who were aware, were knowledgeable about Epidiolex® / Epidyolex®. This was confirmed by the 'True or False' statements as all five statements mostly received correct answers.

4.3.2 Perceptions and barriers of CBD

Results demonstrate that the majority of healthcare professionals (n=90) believe that Epidyolex® should be available in Malta. Healthcare professionals aged between 18-25 years and who have been practicing their profession for 1-5 years believe that CBD products intended for medicinal use without a marketing authorization should be legally available in Malta. Healthcare professionals (n=32) who believe that Epidyolex® should

be available in Malta also think that CBD products intended for medicinal use, without a marketing authorisation, should also be legally available in Malta.

If CBD products were to be legally available in Malta, healthcare professionals (n=101) believe that they should be classified as POM, without the need for a 'green' prescription and control card. Findings demonstrate that healthcare professionals do not perceive CBD as a gateway drug nor that it should be classified as a dangerous or harmful drug. Healthcare professionals (n=67) believe that CBD products used for recreational purposes should be decriminalised. CBD is qualified as a novel food and under European law it is not considered a narcotic drug (Brunetti et al., 2020). However, members of the healthcare professionals (n=58) believe that CBD products should be considered as dangerous drugs and should be prescribed using a 'green' prescription and a control card. The results indicate that healthcare professionals who have been practising their profession for less than 10 years believe that CBD should be classified as OTC or as general sales.

Results demonstrate that healthcare professionals are in agreement that CBD products for medicinal use should be available for prescribing or recommending. These results are in agreement with the study carried out by Schilling et al., (2021), where patients stated that they would feel more comfortable if healthcare professionals prescribed CBD products for use. The majority of healthcare professionals (n=104) would feel comfortable in prescribing or recommending CBD products in painful conditions followed by insomnia (n=75), cancer (n=68) and anxiety (n=67). Pharmacists feel more comfortable in recommending CBD for painful conditions than the other healthcare professions. Schizophrenia, autism, hypertension and AD were the conditions where healthcare professionals were the least comfortable in recommending or prescribing CBD. On the contrary, the study carried out by Haug et al., (2016), reported that healthcare professionals would likely recommend CBD in AD, epilepsy and arthritis.

Results demonstrate that healthcare professionals agree that there are misconceptions among general public about CBD use and that there is a lack of education among the general public about CBD and its use in medical conditions. These findings are in agreement with the study conducted by Leszko and Meenrajan (2021) who demonstrated that the general public often confuse CBD with MC.

Corresponding to the data gathered from the general public questionnaire, healthcare professionals also believe that CBD products used for recreational purposes and for medicinal use should be of the same quality. Healthcare professionals agree that CBD for medicinal use should be manufactured only in appropriately licensed EU GMP certified facilities. In the study conducted by Link et al., (2020), pharmacists were concerned about the level of safety of CBD products available OTC and they're quality consistency.

Findings indicate that healthcare professionals who disagreed that CBD is very safe and has minimal side effects since it is a naturally occurring compound derived from cannabis, do not believe that CBD products intended for medicinal use, without a marketing authorisation, should not be available in Malta.

The Kruskal Wallis test displayed that healthcare professionals that would classify CBD products as general sales (n=11) do not believe that CBD products should only be considered if there is no viable alternative medicine. Instead, they believe and agree that CBD products should be prescribed or recommended for minor ailments (e.g., headache, joint pain, minor sleep disorders) in preference to conventional medicine. Consumers have reported CBD products to be useful and effective in treating conditions such as chronic pain, arthritis and mental health disorders (Corroon and Phillips, 2018; Leas et al., 2020; Fortin et al., 2021; McFadden and Malone, 2021).

Results demonstrate that healthcare professionals (n=97), the majority being pharmacists (n=50), believe that if CBD were to be legally available in Malta, personal beliefs of healthcare professionals would pose as the highest potential barrier.

4.4 Limitations of the study

The systematic literature search included different levels of evidence since experimental and observational studies were included rather than RCTs only. However, this could have reduced the risk of selection bias and increased heterogeneity. Although validation was carried out, reliability testing of the questionnaires was not conducted. The Likert scale, multiple choice questions and close-ended questions could have lacked certain detail or might have not been adequate to collect the perceptions of the participants. Inclusion of open-ended questions could have gathered more data from the respondents. Dissemination and recruitment of participants was carried out by convenience sampling. This could have led to an inaccurate representation of the population and increased the risk of researcher bias. The questionnaire for healthcare professionals had a small sample size. This could have been due to the questionnaire consisting of a lot of questions which might have led to uncompleted questionnaires or ticking random options. During the development and dissemination of the questionnaires, only four MC products were available hence why in the questionnaire for healthcare professionals only Bedrocan® 22/1, Bediol®, Pedanios® 20/1 and Pedanios® 22/1 were mentioned. Another limitation is that CBD and its legal status is a current matter which is evolving rapidly. During the development and dissemination of the questionnaires, CBD products were not legally available in Malta, therefore some of the questions asked were hypothetical which might have not provided a real opinion or consistent data.

4.5 Future recommendations

Conducting a systematic review or meta-analysis focusing solely on RCTs is recommended to better investigate the science related to CBD. Now that CBD products are legally available in Malta, a questionnaire investigating the participants' experience with the use of CBD is proposed. This will help gather real opinions based on actual experience. Awareness and education about the potential side effects caused by CBD products is proposed.

It is recommended to use larger healthcare professional sample size to accurately represent the population. Focus groups may be carried out, ideally consisting of different healthcare professionals with experience in recommending or prescribing CBD. This will provide a better and more recent insight about the knowledge and perceptions about CBD.

Results demonstrate that healthcare professionals are not knowledgeable about the available MC products and CBD. More focus on raising awareness and increasing education about the available eight MC products and CBD is suggested.

4.6 Conclusion

This section is divided into three aspects: Science, Myths and Realities.

4.6.1 Science

The results gathered from the systematic literature search support that CBD has many recognised targets which produce therapeutic effects and has a promising pharmacological purpose. CBD is a naturally occurring compound derived from cannabis that has beneficial and therapeutic effects and also adverse effects. Further human studies investigating the therapeutic effects need to be carried out on a wider scale.

4.6.2 Myths

One myth related to CBD use is that it does not cause any side effects. According to the general public and healthcare professionals, sedation and somnolence is a common to very common side effect caused by CBD (Sections 3.2.1 and 3.3.1). Another misconception is that CBD can cause a euphoric/ 'high' sensation. The general public are aware that this is a myth as the majority of the participants disagreed with this statement (Section 3.2.1).

This study demonstrates that participants from the general public aged between 18-25 years and having a tertiary level of education were more knowledgeable about CBD than other age groups yet healthcare professionals agree that there is a lack of education and misconceptions among the general public about CBD and its use in medical conditions (Section 3.3.2).

Participants from the general public that had never heard about CBD before and who do not believe that CBD products should be available in Malta, believe that CBD use can lead to the use of more dangerous drugs (e.g., cocaine, heroin). The majority of healthcare professionals and the general public agree that CBD is not a gateway drug and believe that CBD products used for recreational purposes should be decriminalised (Sections 3.2.2 and 3.3.2).

4.6.3 Realities

The fact that there are publications reporting therapeutic effects of CBD is a reality (Section 3.1). The majority of the respondents were aware about CBD mostly from social media/news. It is concluded from the results that the general public and healthcare professionals believe that CBD produces an analgesic effect (Sections 3.2.1 and 3.31). Pharmacists feel more comfortable in recommending CBD for painful conditions than other healthcare professionals.

Healthcare professionals are knowledgeable about Epidiolex® / Epidyolex® and most believe that it should be available in Malta. Healthcare professionals and the general public perceive that CBD products should be POM (Sections 3.2.2 and 3.3.2). Results indicate that CBD products recommended or prescribed by a healthcare professional (e.g., pharmacist, physician, nurse) are more likely to be used by patients, thus healthcare professionals should be able to recommend or prescribe CBD products. Potential barriers related to CBD use identified by participants are social stigma and negative personal beliefs of healthcare professionals.

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Appendix 1

Questionnaires

Cannabidiol (CBD): Science, Myths and Realities – Questionnaire for General Public

Section A: Participant demographics
(Tick where applicable)

Gender	□ Male □ Female □ Other □ Prefer not to say
Age (years)	□ 18-25 □ 26-40 □ 41-60 □ 60+
Level of Education	□ Primary □ Secondary □ Post-Secondary □ Tertiary □ Post-Tertiary
Nationality	□ Maltese □ Other (please specify): _____

Section B: Knowledge about CBD
(Tick where applicable)

1. Have you ever heard about CBD before? □ Yes □ No

   If No, please go to Question 2.
   If Yes, from where?

   □ Social media/News
   □ Conferences
   □ Seminars/Webinars
   □ Colleagues
   □ Scientific Literature
   □ Friends/Family
   □ Healthcare professionals
   □ Other (please specify): _____

2. Have you ever discussed the use and effects of CBD with anyone? □ Yes □ No

   If No, please go to Question 3.
   If Yes, with who?

   □ Colleagues
   □ Friends/Family
   □ Healthcare professionals
   □ Other (please specify): _____

3. Tick your level of agreement with the following statements, from strongly disagree to strongly agree.

Statement	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
CBD and tetrahydrocannabinol (THC) are naturally occurring compounds derived from cannabis					
CBD and THC produce different biological effects because they work differently					
CBD has a lower risk of producing mental effects compared to THC					
In humans, CBD is converted into THC					
CBD is available in several formulations such as oils, oral drops, capsules, creams					
Legality of CBD in the European Union is unclear					
Dosing of CBD products depends on the indication and body weight of individual taking it however there is no standard dose					
CBD products do not interact with other medications					
Stopping the use of CBD might produce withdrawal symptoms					
CBD can cause a euphoric / 'high' sensation					

4. CBD has a therapeutic effect: □ Yes □ No

5. Please tick the therapeutic effects which you think CBD can cause:
(Tick all that apply)

□ Antipsychotic (manages psychosis)
□ Antitumour (prevents or inhibits the formation or growth of tumours)
□ Anxiolytic (reduces anxiety)
□ Anti-inflammatory
□ Antiepileptic (treats epilepsy)
□ Anti-vomiting
□ Antioxidant (prevents or slows damage to cells)
□ Antidepressant (treats depression)
□ Cardiovascular (improves conditions related to the heart and blood vessels)
□ Neuroprotective (protects nerve cells from damage)
□ Pain killer
□ Other (please specify):_____

6. Please tick the side effects which you think CBD can cause:
(Tick all that apply)

□ Aggression
□ Agitation
□ Abnormal behaviour
□ Cough
□ Decreased weight
□ Diarrhoea
□ Decreased appetite
□ Drooling
□ Fever
□ Fatigue
□ Infections e.g., bronchitis, urinary tract infection
□ Irritability
□ Increased appetite
□ Liver disorders
□ Rash
□ Sedation and drowsiness
□ Sleep disorders
□ Tremor
□ Vomiting
□ Other (please specify):_____

Section C: Perceptions about CBD

1. Do you think that CBD products intended for medicinal use, should be legally available in Malta?

   □ Yes □ No □ Not sure

2. If CBD products (e.g., oils, capsules) were to be legally available in Malta, which category do you think they should be classified in? (Tick only one)

   □ Prescription-Only Medicine (POM)
   □ Over-the-Counter (OTC) / Pharmacy only Medicine
   □ General Sales Medicine e.g., may be bought from retail shops such as health shops

3. Tick your level of agreement with the following statements should CBD containing products be legally available in Malta; from strongly disagree to strongly agree.

Statement	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
CBD products available in health shops and pharmacies are of the same quality, safety and efficacy					
Potential use of CBD might cause judgement or conflicts between healthcare professionals and patients					
CBD products should not be used due to potential impairing effects on driving					
CBD should only be legally available in pharmacies					
CBD should be legally available in health shops, grocery shops and other retail shops					
CBD products recommended or prescribed by a healthcare professional (e.g., pharmacist, physician, nurse) are more likely to be used by patients					

CBD products should be used in preference to conventional medicine					
CBD products should be used for minor ailments (e.g., headache, joint pain, minor sleep disorders)					
CBD products should be used for major medical conditions (e.g., mental illness, epilepsy, cancer)					
CBD should be classified as a dangerous or harmful drug					
Healthcare professionals should be able to recommend or prescribe CBD products					
CBD products intended for medicinal use should only be considered if there is no viable alternative medicine					
CBD is very safe and has minimal side effects since it is a naturally occurring compound derived from cannabis					
CBD use can lead to the use of more dangerous drugs (e.g., cocaine, heroin)					
CBD products used for recreational purposes should be decriminalised					

Section D: Barriers related to CBD

1. If CBD products intended for medicinal use were to be legally available in Malta, which of the following do you think would pose as potential barriers to CBD use?

   (Tick all that apply)

   □ Access to CBD products from the community pharmacy
   □ Cost of CBD formulations
   □ Risk of impaired driving
   □ Limited scientific data of therapeutic benefits of CBD use
   □ Misuse of CBD products
   □ Personal beliefs of healthcare professionals
   □ Social stigma associated with use of CBD for medicinal use

Cannabidiol (CBD): Xjenza, Miti u Realtajiet – Kwestjonarju għall-Pubbliku Ġenerali

Taqsima A: Tagħrif demografiku dwar il-parteċipant/a
(Immarka fejn japplika)

Sess	□ Maskil □ Femminil □ Newtru □ Nippreferi ma ngħidx
Età (snin)	□ 18-25 □ 26-40 □ 41-60 □ 60+
Livell ta' Edukazzjoni	□ Primarja □ Sekondarja □ Post-Sekondarja □ Terzjarja □ Post-Terzjarja
Nazzjonalità	□ Malti/ja □ Oħra (jekk jogħġbok speċifika): _____

Taqsima B: Għarfien dwar is-CBD
(Immarka fejn japplika)

1. Qatt smajt dwar is-CBD qabel ? □ Iva □ Le

   Jekk Le, jekk jogħġbok għaddi għal mistoqsija 2.
   Jekk Iva, minn fejn?

   □ Midja soċjali/Aħbarijiet
   □ Konferenzi
   □ Seminars/Webinars
   □ Kollegi
   □ Letteratura xjentifika
   □ Ħbieb/Familja
   □ Professjonisti tal-kura tas-saħħa
   □ Oħrajn (jekk jogħġbok speċifika):_____

2. Qatt iddiskutejt l-użu u l-effetti tas-CBD ma' xi ħadd? □ Iva □ Le

   Jekk Le, jekk jogħġbok għaddi għal mistoqsija 3.
   Jekk Iva, ma' min?

   □ Kollegi
   □ Ħbieb/Familja
   □ Professjonisti tal-kura tas-saħħa
   □ Oħrajn (jekk jogħġbok speċifika):_____

3. Ikklassifika kemm taqbel ma’ dawn l-istqarrijiet, minn *Ma naqbilx bil-ħafna* sa *Naqbel ħafna*.

Stqarrija	Ma naqbilx bil-ħafna	Ma naqbilx	La naqbel u lanqas ma naqbilx	Naqbel	Naqbel ħafna
Is-CBD u t-*tetrahydrocannabinol* (THC) huma komposti naturali miksuba mill-kannabis					
Is-CBD u t-THC jipproduċu effetti bijoloġiċi differenti minħabba li jaħdmu b’mod differenti					
Is-CBD għandu riskju aktar baxx li jipproduċi effetti mentali meta mqabbel mat-THC					
Fil-bnedmin, is-CBD jinbidel f’THC					
Is-CBD huwa disponibbli f'diversi formulazzjonijiet bħal żjut, qtar orali, kapsuli, kremi					
Il-legalità tas-CBD fl-Unjoni Ewropea mhix ċara					
Id-dożaġġ ta’ prodotti tas-CBD jiddependi fuq l-indikazzjoni u l-piż ta’ ġisem l-individwu li jużah, madankollu m'hemmx doża fissa					
Prodotti tas-CBD ma jinteraġixxux ma’ mediċini oħra					
It-twaqqif tal-użu tas-CBD jista’ jwassal għal sintomi tal-astinenza					
Is-CBD jista’ jikkawża sensazzjoni ewforika / *high*					

4. Is-CBD għandu effett terapewtiku: Iva Le

5. Jekk jogħġbok immarka l-effetti terapewtiċi li taħseb li għandu jikkawża s-CBD: (Immarka dak kollu li japplika)

 Antipsikotiku (jimmaniġġja l-psikożi)
 Antitumur (jipprevjeni jew jinibixxi l-formazzjoni jew it-tkabbir ta' tumuri)
 Ansjolitiku (inaqqas l-ansjetà)
 Antiinfjammatorju
 Antiepilettiku (jittratta l-epilessija)
 Antiossidant (jipprevjeni jew inaqqas il-ħsara taċ-ċelloli)
 Antidipressiv (jittratta d-depressjoni)
 Inaqqas l-uġigħ
 Kardjovaskulari (ittejjeb il-kundizzjonijiet relatati mal-qalb u l-vini)
 Kontra r-remettar
 Newroprotettiv (jipproteġi ċ-ċelloli tan-nervituri mill-ħsara)
 Oħrajn (jekk jogħġbok speċifika):

_____

6. Jekk jogħġbok immarka l-effetti sekondarji li taħseb li għandu jikkawża s-CBD: (Immarka dak kollu li japplika)

 Aggressjoni
 Aġitazzjoni
 Dijarrea
 Deni
 Disturb fl-irqad
 Għeja
 Infezzjonijiet eż.,bronkite, infezzjoni urinarja
 Imġiba anormali
 Irritabilità
 Problemi fil-fwied
 Raxx
 Remettar
 Rogħda
 Sedazzjoni u ħedla
 Sogħla
 Tilgħib
 Tnaqqis fil-piż
 Tnaqqis fl-aptit
 Żieda fl-aptit
 Oħrajn (jekk jogħġbok speċifika):

_____

Taqsima Ċ: Perċezzjonijiet dwar is-CBD

1. Taħseb li prodotti tas-CBD maħsuba għall-użu mediċinali, għandhom ikunu legalment disponibbli f'Malta?

   □ Iva □ Le □ M'iniex ċert/a

2. Kieku l-prodotti tas-CBD (eż., żjut, kapsuli) ikunu legalment disponibbli f'Malta, f'liema kategorija taħseb li għandhom jiġu kklassifikati? (Immarka waħda biss)

   □ *Prescription-Only Medicine (POM)*/ Mediċini bir-riċetta
   □ *Over-the-Counter (OTC)* / Mediċina li ssib fi spiżerija bla riċetta
   □ *General Sales Medicine* eż., jistgħu jinxtraw minn ħwienet bl-imnut bħal ħwienet tas-saħħa

3. Ikklassifika kemm taqbel ma' dawn l-istqarrijiet kieku l-prodotti li jkollhom is-CBD kellhom ikunu legalment disponibbli f'Malta; minn *Ma naqbilx bil-ħafna* sa *Naqbel ħafna*

Stqarrija	**Ma naqbilx bil-ħafna**	**Ma naqbilx**	**La naqbel u lanqas ma naqbilx**	**Naqbel**	**Naqbel ħafna**
Prodotti tas-CBD disponibbli fil-ħwienet tas-saħħa u fl-ispiżeriji huma tal-istess kwalità, sigurtà u effettività					
L-użu potenzjali tas-CBD jista 'jikkawża ġudizzju jew kunflitti bejn il-professjonisti tal-kura tas-saħħa u l-pazjenti					
Prodotti tas-CBD m'għandhomx jintużaw minħabba li potenzjalment jistgħu jfixklu fis-sewqan					
Is-CBD għandu jkun legalment disponibbli fl-ispiżeriji biss					
Is-CBD għandu jkun legalment disponibbli fi ħwienet tas-saħħa, ħwienet tal-merċa u ħwienet oħra tal-imnut					
Prodotti tas-CBD rakkomandati jew preskritti minn professjonist tal-kura tas-saħħa (eż., spiżjar, tabib, infermier) għandhom probabbiltà li jintużaw aktar mill-pazjenti					

Prodotti tas-CBD għandhom jintużaw bi preferenza għall-mediċina konvenzjonali					
Prodotti tas-CBD għandhom jintużaw għal mard minuri (eż., uġigħ ta' ras, uġigħ fil-ġogi, disturbi minuri fl-irqad)					
Prodotti tas-CBD għandhom jintużaw għal kundizzjonijiet mediċi maġġuri (eż., mard mentali, epilessija, kanċer)					
Is-CBD għandu jkun ikklassifikat bħala droga perikoluża jew ta' ħsara					
Professjonisti fil-kura tas-saħħa għandhom ikunu jistgħu jirrakkomandaw jew jippreskrivu prodotti tas-CBD					
Prodotti tas-CBD maħsuba għall-użu mediċinali għandhom jitqiesu jekk m'hemmx għażla oħra					
Is-CBD huwa sigur ħafna u għandu effetti sekondarji minimi peress li huwa kompost naturali li ġej mill-kannabis					
L-użu tas-CBD jista` jwassal għall-użu ta' drogi aktar perikoluża (eż., kokaina, eroina)					
Prodotti tas-CBD użati għal skopijiet ta' rikreazzjoni għandhom jiġu dekriminalizzati					

Taqsima D: Ostakli marbuta mas-CBD

1. Jekk prodotti tas-CBD maħsuba għall-użu mediċinali jkunu legalment disponibbli f'Malta, liema minn dawn li ġejjin taħseb li potenzjalment jistgħu joħolqu ostaklu tal-użu tas-CBD?

   (Immarka dak kollu li japplika)

   - □ Aċċess għal prodotti tas-CBD mill-ispiżerija tal-komunità
   - □ Prezz tal-formulazzjonijiet tas-CBD
   - □ Riskju ta' nuqqas ta' ħila fis-sewqan
   - □ Data xjentifika limitata b'rabta mal-benefiċċji terapewtiċi tal-użu tas-CBD
   - □ Użu ħażin ta' prodotti tas-CBD
   - □ Twemmin personali ta' professjonisti fil-kura tas-saħħa
   - □ Stigma soċjali marbuta mal-użu tas-CBD għal użu mediċinali

Cannabidiol (CBD): Science, Myths and Realities –Questionnaire for Healthcare Professionals

Section A: Participant demographics
(Tick where applicable)

Gender	□ Male □ Female □ Other □ Prefer not to say
Age (years)	□ 18-25 □ 26-40 □ 41-60 □ 60+
Level of Education	□ Primary □ Secondary □ Post-Secondary □ Tertiary □ Post-Tertiary
Nationality	□ Maltese □ Other (please specify): _____
Profession	□ Dentist □ Medical Doctor □ Nurse □ Pharmacist □ Pharmacy Technician □ Physiotherapist □ Other (please specify): _____
Years of Practice	□ 1-5 □ 6-10 □ 11-20 □ 21-30 □ >30

Section B: Knowledge about CBD
(Tick where applicable)

1. Have you ever heard about CBD before? □ Yes □ No

   If No, please go to Question 2.
   If Yes, from where?

   □ Social media/News
   □ Conferences
   □ Seminars/Webinars
   □ Colleagues
   □ Scientific Literature
   □ Friends/Family
   □ Patients
   □ Other (please specify): _____

2. Has a patient ever asked you about CBD and its use? □ Yes □ No

3. How knowledgeable are you about the following subjects? (Tick according to your level of knowledge, from not knowledgeable to extremely knowledgeable)

Subject	Not knowledge-able	Somewhat knowledge-able	Moderately knowledge-able	Very knowledge-able	Extremely knowledge-able
Mechanism of action of CBD					
Mechanism of action of tetrahydro-cannabinol (THC)					
The different biological effects of CBD and THC					
The different toxic effects of CBD and THC					
The different therapeutic effects of CBD and THC					
EMA approved indications of CBD					
FDA approved indications of CBD					
THC:CBD ratio of Bediol®					
THC:CBD ratio of Bedrocan®					
THC:CBD ratio of Pedanios 20/1®					
THC:CBD ratio of Pedanios 22/1®					
Pharmacology of CBD					
Safety profile of CBD use (e.g., contraindications, cautions, drug interactions)					
Likelihood of dependence or addiction from CBD use					

Effects of CBD use on driving					
Likelihood of withdrawal symptoms upon stopping use of CBD					
Legal status of CBD in Malta					
Legal status of CBD in other European countries					

4. Please tick the therapeutic effects which you think CBD can cause and the probability of such therapeutic effect being produced. (Tick all that apply)

   (The higher the probability number or percentage of an effect, the more likely is it that the therapeutic effect will be caused)

□ Anxiolytic	□0%	□1-20%	□21-40%	□41-60%	□61-80%	□80-100%
□ Antipsychotic	□0%	□1-20%	□21-40%	□41-60%	□61-80%	□80-100%
□ Antitumour	□0%	□1-20%	□21-40%	□41-60%	□61-80%	□80-100%
□ Analgesic	□0%	□1-20%	□21-40%	□41-60%	□61-80%	□80-100%
□ Anti-inflammatory	□0%	□1-20%	□21-40%	□41-60%	□61-80%	□80-100%
□ Antiepileptic	□0%	□1-20%	□21-40%	□41-60%	□61-80%	□80-100%
□ Antiemetic	□0%	□1-20%	□21-40%	□41-60%	□61-80%	□80-100%
□ Antioxidant	□0%	□1-20%	□21-40%	□41-60%	□61-80%	□80-100%
□ Antidepressant	□0%	□1-20%	□21-40%	□41-60%	□61-80%	□80-100%
□ Cardiovascular	□0%	□1-20%	□21-40%	□41-60%	□61-80%	□80-100%
□ Neuroprotective	□0%	□1-20%	□21-40%	□41-60%	□61-80%	□80-100%
□ Other (please specify):	□0%	□1-20%	□21-40%	□41-60%	□61-80%	□80-100%

5. Please tick the side effects which you think CBD can cause and the frequency of such side effect:

   (Tick all that apply)

   Frequencies are defined as follows: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1000) and very rare (< 1/10,000)

□ Aggression	□Very common □Common □Uncommon □Rare □Very rare
□ Agitation	□Very common □Common □Uncommon □Rare □Very rare
□ Abnormal behaviour	□Very common □Common □Uncommon □Rare □Very rare
□ Cough	□Very common □Common □Uncommon □Rare □Very rare
□ Decreased weight	□Very common □Common □Uncommon □Rare □Very rare
□ Diarrhoea	□Very common □Common □Uncommon □Rare □Very rare
□ Decreased appetite	□Very common □Common □Uncommon □Rare □Very rare
□ Drooling	□Very common □Common □Uncommon □Rare □Very rare
□ Fever	□Very common □Common □Uncommon □Rare □Very rare
□ Fatigue	□Very common □Common □Uncommon □Rare □Very rare
□Infections e.g., bronchitis, urinary tract infection	□Very common □Common □Uncommon □Rare □Very rare
□ Irritability	□Very common □Common □Uncommon □Rare □Very rare
□ Increased appetite	□Very common □Common □Uncommon □Rare □Very rare
□ Liver disorders	□Very common □Common □Uncommon □Rare □Very rare
□ Rash	□Very common □Common □Uncommon □Rare □Very rare
□ Sedation, somnolence	□Very common □Common □Uncommon □Rare □Very rare
□ Sleep disorders	□Very common □Common □Uncommon □Rare □Very rare
□ Tremor	□Very common □Common □Uncommon □Rare □Very rare
□ Vomiting	□Very common □Common □Uncommon □Rare □Very rare
□Other (please specify):	□Very common □Common □Uncommon □Rare □Very rare

6. Are you aware that there is only one FDA and EMA approved, CBD-based product called Epidiolex® / Epidyolex®?

   □ Yes □ No □ Not sure

   If No, please go to Section C.
   If Yes or Not sure, please answer the following statements by ticking 'True' or 'False, then go to Section C.

   a) Epidyolex® is indicated for the treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome, in conjunction with clobazam, for patients 2 years of age and older

      □ True □ False

   b) Epidyolex® is only available as a 100mg/ml oral solution

      □ True □ False

   c) Dosing of Epidyolex® is weight dependent and the dose should be increased in weekly increments

      □ True □ False

   d) Before starting Epidyolex®, a baseline liver function test has to be carried out

      □ True □ False

   e) The exact mechanisms by which Epidyolex® exerts its anticonvulsant effect in humans are unknown

      □ True □ False

Section C: Perceptions about CBD
(Tick where applicable)

1. Do you think that Epidyolex® should be available in Malta?

   □ Yes □ No □ Not sure

2. Do you think that CBD products intended for medicinal use, without a marketing authorisation, should be legally available in Malta?

   □ Yes □ No □ Not sure

3. If CBD products (e.g., oils, capsules) were to be legally available in Malta, which category do you think they should be classified in? (Tick only one)

   - □ Prescription-Only Medicine (POM)
   - □ Over-the-Counter (OTC) / Pharmacy only Medicine
   - □ General Sales Medicine e.g., may be bought from retail shops such as health shops

4. If CBD products were to be legally available in Malta and were to be classified as POM, do you think that they should be:
   (Tick only one)

   - □ Prescribed using a 'green' prescription and control card?
   - □ Prescribed without the need for a 'green' prescription and control card?
   - □ Prescribed following the same procedure for medical cannabis where a licenced medical practitioner has to obtain approval from the Superintendent of Public Health?

5. If CBD was to be legally available, would you feel comfortable in prescribing or recommending its use in the following conditions:
   (Tick where applicable)

Anxiety	□ Yes □ No □ Maybe
Arthritis	□ Yes □ No □ Maybe
Alzheimer's Disease	□ Yes □ No □ Maybe
Autism	□ Yes □ No □ Maybe
Cancer	□ Yes □ No □ Maybe
Depression	□ Yes □ No □ Maybe
Epilepsy	□ Yes □ No □ Maybe
Hypertension	□ Yes □ No □ Maybe
Inflammation	□ Yes □ No □ Maybe
Insomnia	□ Yes □ No □ Maybe
Migraine	□ Yes □ No □ Maybe
Multiple Sclerosis	□ Yes □ No □ Maybe
Nausea and vomiting	□ Yes □ No □ Maybe
Pain	□ Yes □ No □ Maybe
Parkinson's Disease	□ Yes □ No □ Maybe
Post-Traumatic Stress Disorder (PTSD)	□ Yes □ No □ Maybe
Schizophrenia	□ Yes □ No □ Maybe
Skin conditions e.g., eczema, psoriasis	□ Yes □ No □ Maybe

6. Tick your level of agreement with the following statements, from strongly disagree to strongly agree.

Statement	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
There is a lack of education among the general public about CBD and its use in medical conditions					
There is not enough data about the side effects of CBD products					
CBD products for medicinal use should be available for prescribing or recommending					
CBD products should only be legally available in pharmacies					
CBD products should be legally available in health shops, grocery shops and other retail shops					
CBD products should not be prescribed or recommended due to potential impairing effects on driving					
CBD products should be prescribed or recommended for minor ailments (e.g., headache, joint pain, minor sleep disorders) in preference to conventional medicine					
CBD is very safe and has minimal side effects since it is a naturally occurring compound derived from cannabis					
CBD products intended for medicinal use should only be considered if there is no viable alternative medicine					
CBD products should be available on prescription only, to avoid misuse and abuse of such products					

CBD should be classified as a dangerous or harmful drug					
There are misconceptions among the general public about CBD use					
Healthcare professionals are concerned about a patient's perception of a healthcare professional prescribing or recommending CBD for medicinal use					
CBD use will lead to the use of more dangerous drugs (e.g., cocaine, heroin)					
CBD for medicinal use should be manufactured only in appropriately licensed EU GMP certified facilities					
The quality between CBD products used for recreational purposes and for medicinal use should be the same					
CBD products used for recreational purposes should be decriminalised					

Section D: Barriers related to CBD

1. If CBD products intended for medicinal use were to be legally available in Malta, which of the following do you think would pose as potential barriers to CBD use?

   (Tick all that apply)

   □ Access to CBD products from the community pharmacy
   □ Cost of CBD formulations
   □ Risk of impaired driving
   □ Limited scientific data of therapeutic benefits of CBD use
   □ Misuse of CBD products
   □ Personal beliefs of healthcare professionals
   □ Social stigma associated with use of CBD for medicinal use

Appendix 2

Information Sheets

L-Università ta' Malta

Participants' Information Sheet

Dear Participant,

My name is Abigail Calleja and I am currently reading for a Doctorate in Pharmacy, at the University of Malta. I am presently conducting a research study for my doctoral thesis entitled, CBD: Science, Myths and Realities, under the supervision of Professor Anthony Serracino-Inglott. This letter is an invitation to participate in this study. Below you will find information about the study and about what your involvement would entail, should you decide to take part.

The aim of my study is to assess the perception of the general public and healthcare professionals about cannabidiol (CBD). Your participation in this study would help gain insight about the perception regarding the potential use of CBD. Any data collected from this research will be used solely for purposes of this study.

Should you choose to participate, you will be asked to take part in a questionnaire. Given consent constitutes by filling in and returning the questionnaire. I declare that you will remain anonymous. The questionnaire will not, in any way, collect personal information nor your identity. Completion of the questionnaire should not take longer than 10 minutes. Data collected will be accessed only by the researcher and the data will be stored on the researcher's personal computer that is password protected. Any questionnaires in hard-copy form will be placed in a locked cupboard.

Participation is entirely voluntary and you have the right to withdraw or stop from the questionnaire at any time, without needing to give reason. Furthermore, withdrawal from the study will not have any negative repercussions on you and any data collected will be erased. Data will continue to be stored anonymously if it is impossible to delete. If you choose to participate, please note that there are no direct benefits to you. Your participation does not entail any known or anticipated risks. Once the study is completed, the data will be erased.

A copy of this information sheet is being provided for you to keep and for future reference.

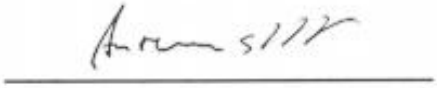
This study has been approved by the Research Ethics Committee of the Faculty of Health Sciences at the University of Malta.

Thank you for your time and consideration. Should you have any questions or concerns, please do not hesitate to contact me on +356 79991996 or by e-mail abigail.m.calleja.14@um.edu.mt or my supervisor Professor Anthony Serracino-Inglott on anthony.serracino-inglott@um.edu.mt.

Yours sincerely,

Abigail Calleja

Researcher



Professor Anthony Serracino-Inglott

Research Supervisor

L-Università ta' Malta

Formula ta' Informazzjoni għall-Parteċipanti

Għażiż/a Parteċipant/a,

Jiena jisimni Abigail Calleja, fil-preżent qed insegwi id-Dottorat fil-Farmaċija, fl-Università ta' Malta. Bħalissa qed immexxi studju ta' riċerka għat-teżi tad-dottorat tiegħi intitolata, *CBD: Science, Myths and Realities,* taħt is-superviżjoni tal-Professur Anthony Serracino-Inglott. Din l-ittra hija stedina biex tipparteċipa f'dan l-istudju. Jekk tiddeċiedi li tieħu sehem, hawn taħt għandek issib informazzjoni dwar l-istudju u dwar dak li jinvolvi l-involviment tiegħek.

L-għan tal-istudju tiegħi huwa li nevalwa l-perċezzjoni tal-pubbliku ġenerali u l-professjonisti tal-kura tas-saħħa dwar il-*cannabidiol* (CBD). Il-parteċipazzjoni tiegħek f'dan l-istudju tgħin biex tikseb għarfien dwar il-perċezzjoni rigward l-użu potenzjali tas-CBD. Id-dejta miġbura minn din ir-riċerka se tintuża biss għal skopijiet ta' dan l-istudju.

Jekk tagħżel li tipparteċipa, tkun mitlub/a tieħu sehem fi kwestjonarju. Il-kunsens mogħti jikkostitwixxi biliti timla u tirritorna l-kwestjonarju. Niddikjara li inti tibqa' anonimu/a. Il-kwestjonarju bl-ebda mod ma jiġbor informazzjoni personali u lanqas l-identità tiegħek. Tlestija' tal-kwestjonarju m'għandux jieħu aktar minn 10 minuti. Id-dejta miġbura se tkun aċċessata mir-riċerkatriċi biss u d-dejta se tinħażen fuq il-kompjuter personali tar- riċerkatriċi li huwa protett bil-password. Barra minn hekk, il-kwestjonarju stampat se jinqafel f'post sigur.

Il-parteċipazzjoni hija kompletament volontarja u għandek id-dritt li tirtira jew tieqaf mill-kwestjonarju fi kwalunkwe ħin, mingħajr ma jkollok bżonn tagħti raġuni. Barra minn hekk, l-irtirar mill-istudju ma jkollux riperkussjonijiet negattivi fuqek u kwalunkwe dejta miġbura titħassar. Id-dejta tibqa' tinħażen b'mod anonimu kemm-il darba jkun impossibbli li titħassar. Jekk tagħżel li tipparteċipa, jekk jogħġbok innota li m'hemm l-ebda benefiċċju dirett għalik. Il-parteċipazzjoni tiegħek ma tinvolvi l-ebda riskju magħruf jew antiċipat.Id-dejta kollha miġbura titħassar mat-tlestija tal-istudju.

Kopja ta' din l-ittra ta' informazzjoni qed tiġi pprovduta għalik biex iżżommha u għal referenza futura.

Dan l-istudju ġie approvat mill-Kumitat għall-Etika fir-Riċerka fi ħdan il-Fakultà tax-Xjenzi tas-Saħħa fl-Università ta' Malta.

Grazzi tal-ħin u l-konsiderazzjoni tiegħek. Jekk għandek xi mistoqsijiet jew tħassib, jekk jogħġbok, toqgħodx lura milli tikkuntattjani fuq +356 79991996 jew tibgħatli e-mail fuq abigail.m.calleja.14@um.edu.mt. Tista' wkoll tikkuntattja lis-Superviżur Professor Anthony Serracino-Inglott billi tibgħat email fuq anthony.serracino-inglott@um.edu.mt.

Dejjem tiegħek,

Abigail Calleja

Riċerkatriċi

Professor Anthony Serracino-Inglott

Superviżur tar-riċerka

Appendix 3

Validation Sheet

Validation Sheet for Questionnaire

This tool asks for your honest evaluation of the questionnaire which will be used in the data gathering for the study 'CBD: Science, Myths and Realities'.

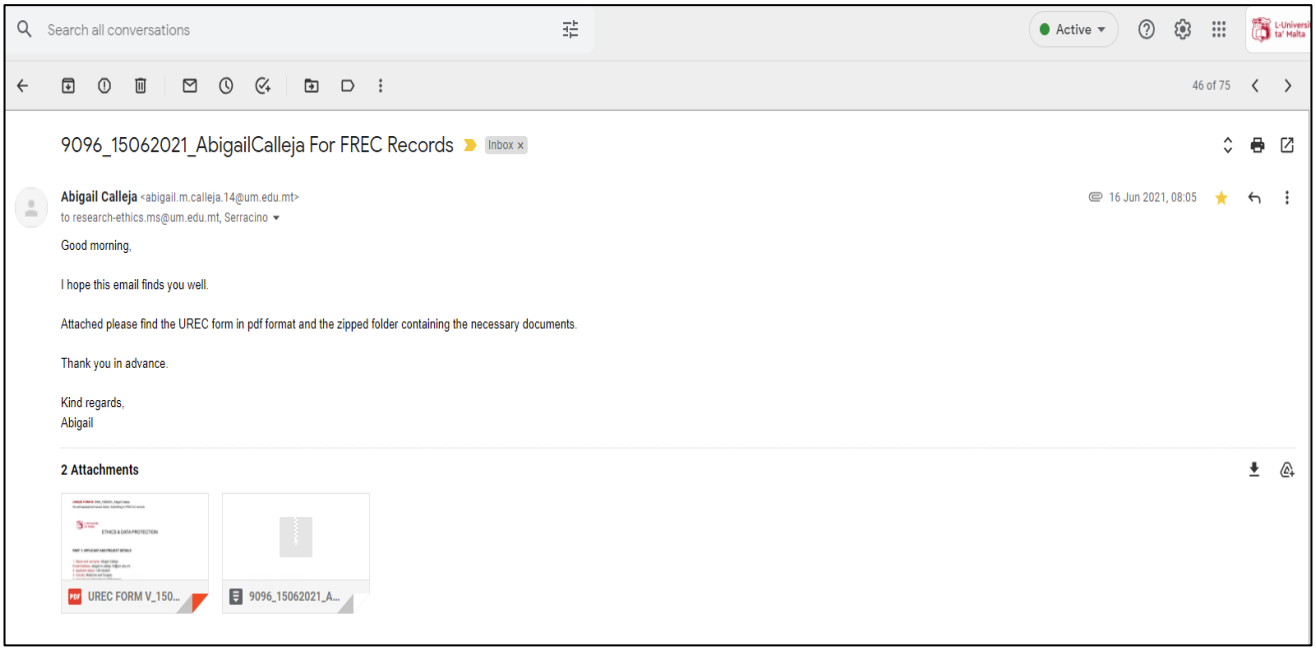
(Tick your level of agreement with the following statements, from strongly disagree to strongly agree)

Statement	**Strongly disagree**	**Disagree**	**Neither agree nor disagree**	**Agree**	**Strongly agree**
The sequencing of the questions is logical					
The questions are presented and organised in a meaningful manner					
The questions are comprehensive enough to collect all the information needed to address the purpose and goals of the study					
The questions are worded in a clear, concise and unambiguous manner					
The questions are necessary, appropriate and not repetitive					
The layout is easy to read and pleasant on the eye					
The questions asked are not too personal nor of a potentially embarrassing nature					

Would you like to make any other comments of further suggestions for improvement?

Appendix 4

Research Ethics approval


Search all conversations
Active
46 of 75
9096_15062021_AbigailCalleja For FREC Records
Inbox x
Abigail Calleja <abigail.m.calleja.14@um.edu.mt>
to research-ethics.ms@um.edu.mt, Serracino
16 Jun 2021, 08:05
Good morning,
I hope this email finds you well.
Attached please find the UREC form in pdf format and the zipped folder containing the necessary documents.
Thank you in advance.
Kind regards,
Abigail
2 Attachments
UREC FORM V_150...
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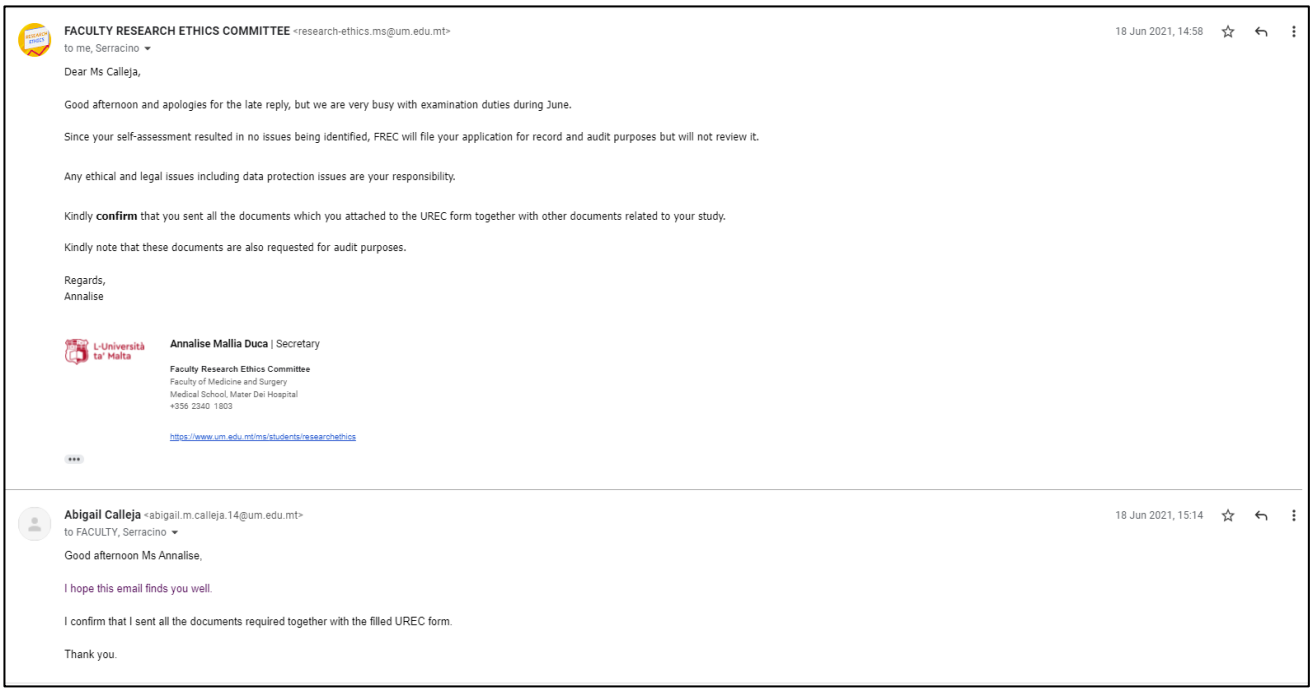
FACULTY RESEARCH ETHICS COMMITTEE <research-ethics.ms@um.edu.mt>
to me, Serracino
18 Jun 2021, 14:58
Dear Ms Calleja,
Good afternoon and apologies for the late reply, but we are very busy with examination duties during June.
Since your self-assessment resulted in no issues being identified, FREC will file your application for record and audit purposes but will not review it.
Any ethical and legal issues including data protection issues are your responsibility.
Kindly confirm that you sent all the documents which you attached to the UREC form together with other documents related to your study.
Kindly note that these documents are also requested for audit purposes.
Regards,
Annalise
L-Università ta' Malta
Annalise Mallia Duca | Secretary
Faculty Research Ethics Committee
Faculty of Medicine and Surgery
Medical School, Mater Dei Hospital
+356 2340 1803
https://www.um.edu.mt/ms/students/researchethics
Abigail Calleja <abigail.m.calleja.14@um.edu.mt>
to FACULTY, Serracino
18 Jun 2021, 15:14
Good afternoon Ms Annalise,
I hope this email finds you well.
I confirm that I sent all the documents required together with the filled UREC form.
Thank you.

Appendix 5

CBD effects on mental health disorders

Study	Effect being studied	Type of study	Subject used	CBD strength	Summary of method	Main findings
Hallak et al., 2010	Effects of CBD on selective attention in schizophrenic patients	Clinical trial	Humans	CBD (300 or 600mg)	Twenty-eight schizophrenic patients were subjected to the Stroop colour word test. The first one was carried out without drugs, in the second one, the participants were split into three groups where they received CBD (300 or 600mg) or placebo. The test was then performed again and the results were compared	There were no significant differences with regards to electrodermal measures. Overall performance was improved in all three groups, with the control group and the group who received 300mg CBD performing the best. A decrease in the number of errors was experienced the most in these two groups
Bergamaschi et al., 2011	Effects of CBD on generalised social anxiety	RCT	Humans	CBD (600mg)	Healthy patients (control group) and treatment naïve patients with generalised social anxiety disorder were either administered CBD (600mg) or placebo one hour and a half before performing the simulated public speaking test (SPST)	CBD greatly decreased anxiety, cognitive impairment, discomfort in speech performance and the alertness in anticipatory speech. These effects were all increased in the placebo group especially when compared to the control group
Scopinho et al., 2011	Effects on hyperphagia	Animal study	Rats	CBD (1, 10 and 20 mg/kg)	Fed or fasted Wistar rats were administered CBD (1,	CBD did not have any changes on food intake in the fed and fasted

				intraperitoneal (IP)	10 and 20mg/kg) and food intake was measured 30 min later for 1 hr. Additional fed or fasted groups received, after pre-treatment with CBD (20 mg/kg) or vehicle, a CB1 receptor agonist (2 mg/kg) or a 5-HT1A receptor agonist (1 mg/kg) and were submitted to the food intake test	groups. It reduced the hyperphagia induced by the CB1 receptor agonist and by the 5-HT1A receptor agonist, in both fed and fasted groups
Uribe- Mariño et al., 2011	Anti-aversive effects of CBD and its effect on response to fear	Animal study	Mice	CBD (0.3, 3, or 30 mg/kg) intraperitoneal (IP)	Mice were placed in an arena, first alone for three days and then together with a snake. Thirty minutes before the snake was placed the mice were administered CBD or placebo subsequently	The mice exhibited defensive behaviour when the snake was placed in the arena. CBD (3, 30mg/kg) decreased the duration and behavioural index of active avoidance when compared to the placebo group. CBD produced an anti-aversive effect, a reduction in explosive escape and a decrease in defensive immobility
Barichello et al., 2012	Effect on cognitive impairments	Animal study	Rats	CBD (2.5, 5, or 10 mg/kg) intraperitoneal (IP)	Placebo or CBD, once or daily for 9 days was administered to rats after meningitis induction	Levels of TNF-alpha, cytokine-induced neutrophil chemoattractant (CINC-1), brain derived neurotrophic factor (BDNF), IL-1beta and IL-6 were

						not altered by acute treatment of CBD. Chronic administration of CBD at different doses reduced the TNF-a level in frontal cortex. Chronic treatment of CBD (10mg/kg) prevented memory impairment in rats with pneumococcal meningitis
Almeida et al., 2013	Anxiolytic effects	Animal study	Wistar rats (WR) and spontaneously hypertensive rats (SHRs)	CBD (1, 5, 15, 30 or 60mg/kg) intraperitoneal (IP)	In experiment 1, rats were administered vehicle or CBD (15, 30 or 60 mg/kg) and after 30 minutes they were subjected to the social interaction test. In experiment 2, the same test was conducted but lower doses of CBD were administered (1, 5 or 15mg/kg)	In experiment 1, CBD reduced social interaction time, higher locomotion frequency and rearing frequencies. These effects were presented more in SHR than in WR. In experiment 2, CBD (1mg/kg) increased the social interaction and passive interaction in WR but not in SHRs. Locomotion frequency and rearing frequency were higher in SHR than in WR. CBD has an anxiolytic effect but not an antipsychotic effect
Campos et al., 2013	Investigating the involvement of hippocampal neurogenesis in	Animal study	Mice	CBD (30mg/kg) intraperitoneal (IP)	The mice (wild type and GFAP-thymidine kinase transgenic mice) underwent a 14 days chronic	CBD prevented the anxiogenic effect of CUS in wild type mice but not GFAP-TK. Adult hippocampal neurogenesis was

	the anxiolytic effect of CBD				unpredictable stress (CUD). CBD or vehicle was administered 2 hours after the daily stressor	increased by CBD. CBD caused an anxiolytic effect in CUS model, which involved the participation of CB1 receptor which led to an increase in anandamide levels. CBD stimulated progenitor proliferation and cell cycle progression via CB1 and CB2 receptors
Seeman, 2016	Effects on dopamine levels and potential antipsychotic effects	In vitro	Rat striatal tissues	CBD (0.1 to 10,000 nM)	Rat striatal tissues were titrated with domperidone and CBD and the effects of CBD on dopamine (D2) receptors was measured	CBD has a biphasic action with regards to competition with domperidone at the brain D2 receptors. The inhibition of the binding of domperidone by CBD was observed. The clinical doses of CBD are enough to occupy functioning D2 high sites which may be the cause for CBD's antipsychotic effects
Shannon and Oplia-Lehman, 2016	Anxiolytic	Case	Female	CBD supplements (25mg) and CBD sublingual spray (6 to 12mg)	A 10-year-old girl suffering from PTSD received CBD supplements (25mg) nocte for 5 months then CBD sublingual spray (6-12mg) was added for during the day	CBD improved sleep and eased mood. Anxiety was reduced

Libro et al., 2017	Effects on Alzheimer's disease (AD)	In vitro	Mesenchymal stem cells derived from gingiva (GMSCs)	CBD (5 µM)	Mesenchymal stem cells were pre-treated with CBD (5 µM) and the effects of CBD were assessed	CBD downregulated expression of the genes linked to AD which are responsible for aberrant tau phosphorylation and for the secretases involved in Aβ generation. CBD upregulated genes related to catabolic protein processes. CBD inhibited GSK3β, an important player in AD pathogenesis, by promoting PI3K/Akt signalling. Vanilloid receptor 1 (TRPV1) mediated the modulatory effect of CBD on PI3K/Akt/GSK3β axis
Osborne et al., 2017	Effect on cognitive deficits in schizophrenia	Animal study	Rats	CBD (10mg/kg)	Time-mated pregnant rats were administered polyinosinic-polycytidilic acid (poly I:C) or control at gestation day 15. Male offspring were injected twice daily with CBD or vehicle for 3 weeks	POLY+VEH offspring produced impaired recognition and working memory together with a decreased social interaction. CBD improved recognition, working memory and social interaction in those rats who were administered poly (I:C)
Bhattacharyya et al., 2018	Neurocognitive mechanism of CBD	RCT	Humans	CBD (600mg)	Seventeen at clinical high risk (CHR) of psychosis received placebo while 16 participants at CHR of	During the encoding phase, CHR participants who were given placebo demonstrated a greater activation in a cluster in the left

					psychosis received a single dose of CBD 600mg. The 19 healthy participants did not receive any drug. Functional magnetic resonance imaging (fMRI) was utilised while the participants performed a verbal learning task	parahippocampal gyrus that extended into the superior temporal gyrus and cerebellum. This group however showed a lower activation in the precentral gyri than the CHR who were given CBD. During the recall stage, the placebo groups showed less activation in 3 clusters with foci in the left cingulate gyrus and the adjacent body of caudate, the right precentral gyrus extending to the cingulate gyrus; and in the medial frontal gyrus, when compared to the CHR plus CBD group. Between group linear analysis showed that across 3 groups of participants, the activation in the CBD group was intermediate compared to the placebo and control groups. There were no differences in task performance. A single dose of CBD may partially normalize dysfunction in the medial temporal lobe, striatum,

						and midbrain in individuals at CHR of psychosis
Gonzalez-Cuevas et al., 2018	Anti-relapse (stress, anxiety, impulsiveness) effects	Animal study	Rats	CBD (2.5 g transdermal gel)	Rats with alcohol or cocaine self-administration histories received transdermal CBD at 24 h intervals for 7 days and various tests were carried out	CBD demonstrated beneficial effects in reducing drug seeking with effects lasting even after treatment. CBD reduced experimental anxiety in rats with alcohol and cocaine histories and it reversed impulsive behaviour in rats with an alcohol dependence history. CBD lacks sedative and nonspecific amotivational effects
Hindocha et al., 2018	Effect on impulse and memory during nicotine abstinence	RCT	Humans	CBD (800mg)	Thirty, cigarette smoking participants received CBD or placebo after an overnight of abstinence	CBD did not improve spatial nor verbal working memory. CBD had no effect on the impulsivity experienced during tobacco abstinence. CBD was not effective in reversing the cognitive impairments related with acute nicotine abstinence
Linares et al., 2018	Effect on anxiety and sleep	RCT	Humans	CBD (300mg)	Twenty-six eligible participants were split into two groups. One group receive placebo on the first night while the second group	There were no differences between CBD and placebo groups with regards to polysomnographic findings or cognitive and subjective measures in a sample of

					received CBD 300mg, 30 minutes before the polysomnographic recording began. Cognitive and subject measures were carried out on the morning after. During the second night the same procedure was done using the drug that had not been administered in the previous night	healthy subjects. CBD did not induce any significant effect
Navarette et al., 2018	Effect on behavioural and gene expression alterations caused by spontaneous cannabinoid withdrawal	Animal study	Mice	CBD (5, 10 and 20mg/kg) intraperitoneal (IP)	CP-55,940 (a cannabinoid receptor agonist) was administered to mice every 12 hours for 7 days. Treatment was stopped and spontaneous cannabinoid withdrawal was evaluated. CBD or the vehicle was administered on the last dose of CP-55,940	Spontaneous cannabinoid withdrawal caused an increase in motor activity and somatic signs. CBD blocked all these symptoms. It normalised the attenuation in the number of groomings. CBD did not have any effect on the somatic signs in vehicle-treated animals. CBD (5, 10 and 20mg/kg) administration in abstinent mice treated the anxiogenic-like effect observed. In the non-abstinent mice, CBD (10 and 20mg/kg) induced an anxiolytic-like effect.

						CBD (5, 10 and 20mg/kg) normalized gene expression changes induced by CP-55,940-mediated spontaneous withdrawal
Peres et al., 2018	Effect on schizophrenia-like behavioural abnormalities	Animal study	Rats	CBD (0.5, 1 or 5mg/kg) intraperitoneal (IP)	Wistar rats (WRs) and spontaneously hypertensive rats (SHRs) were administered CBD or vehicle 30 to 60 days after birth. Three different experiments were carried out	SHRs treated with CBD (0.5mg/kg) prevented the development of increased locomotor activity. CBD did not affect social interaction in SHRs however CBD (1.0 or 5mg/kg) increased social interaction in WRs. Treatment with 0.5mg/kg in SHRs prevented the occurrence of impaired pre-pulse inhibition of startle. SHRs treated with CBD 0.5mg/kg and WRs treated with 1.0mg/kg CBD experienced an increase in freezing response. CBD increased levels of serotonin. CBD did not induce catalepsy nor tardive dyskinesia
Belardo et al., 2019	Effects of CBD on sensorial and neuropsychiatric dysfunctions related to	Animal study	Mice	CBD oil (10% /30 µL)	A weight drop mild TBI mouse model was used. CBD was administered from day 1 to day 14 and from day 50 to day 60	CBD reduced tactile allodynia in mice with TBI. There was no difference in pain response when CBD was administered in sham mice. CBD reduced rearing in

	traumatic brain injury (TBI)					mice with TBI. CBD reduced attacks of aggressive behaviour in mice with TBI. There was no effect in sham mice treated with CBD compared to shame mice treated with vehicle. CBD attenuated the immobility in mice with TBI compared to the vehicle. No change was noted in sham mice. CBD treated mice with TBI, showed improvement in sociability level. CBD normalised the high levels of glutamate and D-Aspartate noted in mice with TBI and in sham mice. CBD increased the levels of GABA which were decreased by TBI. Chronic CBD treatment reduced behavioural dysfunctions
Bolsoni et al., 2019	Effect of CBD on cortisol awakening response in a patient with post-traumatic	Case report	Female	CBD (300mg/day)	A 15-year-old girl who experienced acute sexual violence, was treated with CBD for 7 days. A cortisol awakening response (CAR) test was performed. A behavioural test was	Initial dose of CBD 300mg did not prevent an increase in anxiety, however, 1 week after, daily administration of CBD for 7 days demonstrated an absence of increased anxiety scores. There was an increase in CAR but this

	stress disorder (PTSD)				performed followed by administration of CBD 2.5 hours after the test. CBD treatment continued for 7 days	was decreased when PTSD developed in the patient
Hermush and Ore, 2019	Effect on patient with dementia	Case	Human	CBD oil (20% three times a day for 7 days, then four times a day)	CBD was administered to a patient with dementia, cerebrovascular events and other medical conditions	Patient started to show signs of alertness and responsiveness. CBD attenuated the patient's spasticity
Heussler et al., 2019	Effect on Fragile X syndrome (FXS), neuropsychiatric and behavioural symptoms	Clinical trial	Humans	CBD transdermal gel (50 to 250mg)	Twenty children and adolescents who have FXS were administered CBD twice a day for 12 weeks starting from 50mg and increasing to the maximum dose of 250mg	A significant reduction was noted in anxiety, depression and mood scale (ADAMS) from screening to week 12 and also in the manic/hyperactive behaviour, social avoidance, general anxiety and compulsive behaviour subscales. From screening to week 12, a reduction was also noted in all Aberrant behaviour checklist – community for FXS (ABC-CFXS) subscales such as socially unresponsive/lethargic, hyperactivity and inappropriate speech and in the Paediatric anxiety rating scale (PARS-R),

						paediatric quality of life inventory (PedsQL) and visual analogue scale (VAS) measures
Linares et al., 2019	Effect on anxiety and public speaking	Clinical trial	Humans	CBD (150, 300 or 600mg)	Fifty-seven healthy male participants received 150mg, 300mg, 600mg CBD or placebo. One hour and a half later, the participants were subjected to a simulated public speak test (SPST)	CBD (300mg) decreased anxiety during the speech compared to the placebo
Shannon et al., 2019	Effect on anxiety and insomnia	Case series	Humans	CBD capsule (25mg/day. 50mg/day or 75mg/day if symptoms persisted)	Adult participants received CBD for anxiety and insomnia together with their usual treatment	Within the first month, anxiety levels were decreased by CBD in 79.2% of the patients and remained decreased throughout the study. Sleep was also improved within the first month in 66.7% of the patients and remained constant
Pretzsch et al., 2019a	Effect on autism	RCT	Humans	CBD (600mg)	Seventeen healthy male participants and seventeen male participants with autism were administered placebo or 600mg CBD orally. The fractional amplitude of low-frequency	CBD greatly increased fALFF in the cerebellar vermis and the right fusiform gyrus. It was noted that post-hoc, this effect was predominantly driven by the autistic group, with no important change in controls. In the autistic group, CBD greatly altered vermal

					fluctuations (fALFF) was measured across the brain	functional connectivity together with several of its subcortical and cortical targets. It did not have any effect on fusiform functional connectivity with other regions in either group
Pretzsch et al., 2019b	Effects of CBD on the brain in patients +/- autism	RCT	Humans	CBD (600mg)	Thirty-four men with or without autism were administered CBD (600mg) or placebo as a single dose	CBD affected both glutamate and GABA levels in adults with or without autism, but prefrontal GABA systems in autism react differently. Levels of glutamate were increased in subcortical while decreased in cortical. GABA levels were increased in participants without autism but was decreased in autistic brain
Wilson et al., 2019	Effect on psychosis	RCT	Humans	CBD (600mg)	Thirty-three participants clinical high risk for psychosis (CHR) were administered 600 mg CBD or placebo on the anticipation phase of the monetary incentive delay task (MIDT)	Abnormal activation in the left insula/parietal operculum in CHR participants who received placebo was observed. CBD decreased the increase in activation in the left insula/parietal operculum and CBD was linked with the total slowing of reaction time. CBD may have an antipsychotic effect by normalising motivational

						salience and moderating motor response
Appiah-Kusi et al., 2020	Effect on psychosis and anxiety	RCT	Humans	CBD (600 mg)	Twenty-six healthy controls and 32 clinical high risk for psychosis (CHR) patients participated in the Trier Social Stress Test (TSST). Half of the CHR participants received 600mg/day of CBD while the other half received placebo for a week. Serum cortisol, anxiety and stress related to public speaking were assessed.	The change in cortisol related with the experimental stress exposure was greatest in the healthy participants. The group of CHR who received CBD had an intermediate change and the CHR patients who received placebo had the least change in cortisol. The CHR group administered placebo experienced the greatest level of anxiety in response to the TSST. The least level was among the healthy participants and the group of CHR who received CBD had an intermediate level of anxiety. With regards to the effect of acute stress on negative self-statements, the CHR group plus placebo had the greatest level of experience of negative statements, while the experience was intermediate in the CHR group plus CBD and it was the least in the healthy participants

Bloomfield et al., 2020	Effect in altered memory processing such as Alzheimer's disease, schizophrenia and post-traumatic stress disorder	RCT	Humans	CBD (600mg)	CBD (600mg) or placebo was administered to 15 health patients on separate days. Cerebral blood flow (CBF), working memory and episodic memory were investigated	CBF in the hippocampus was increased by CBD. No differences in memory task performance were noted. There was a significant correlation noted between a reduced reaction time and CBD-induced increases in orbitofrontal CBF. CBD has a potential effect in conditions with altered memory processing
Coles et al., 2020	Effect in Alzheimer's disease (AD)	Animal study	Mice	CBD (5mg/kg) intraperitoneal (IP)	Control (wild type mice) and APPxPS1 transgenic female mice were treated daily with 5mg/kg CBD or vehicle starting 3 weeks before assessing behavioural areas including anxiety, exploration, locomotion, motor functions, cognition and sensorimotor gating.	CBD showed increased rearing. There were no differences in exploration. CBD had no effect on anxiety levels. There were no significant results caused by CBD on motor function. CBD had no overall effect on sensorimotor gating and did not change any genotype effect. Medium dose of CBD demonstrated therapeutic benefits in object recognition deficits in AD patients
Davies et al., 2020	CBD effects on emotional dysregulation and anxiety	RCT	Humans	CBD (600mg)	Thirty-three clinical high risk for psychosis (CHR) patients were administered CBD or placebo and then	During fear processing, CHR patients who received placebo demonstrated a larger activation in the parahippocampal gyrus but a

					they were scanned with functional magnetic resonance imaging (fMRI) during a fearful face processing model. The same method was carried out for nineteen healthy control participants however no drugs were administered	lower activation in the striatum than the control groups. The activation in those patients who received CBD was intermediate compared to the healthy and placebo groups. CBD in CHR patients, affects brain functions in areas which are important in psychosis risk and emotional processing
Gáll et al., 2020	Long term effects of CBD in the chronic unpredictable mild stress (CUMS) model of depression	Animal study	Rats	CBD (10mg/kg) intraperitoneal (IP)	Rats were subjected to different stressors to induce anhedonia and anxiety. CBD or vehicle were administered for 28 days	Weight gain and a higher sucrose preference was observed in CBD treated rats. During the open field test, chronic CBD treated rats demonstrated a higher increase in horizontal and vertical exploration such as rearing, leaning on walls, distance moved. The elevated plus maze test did not reveal any differences between the groups. The effects of CUMS on hair corticosterone were reversed by CBD
Lawn et al., 2020	CBD effect on reward processing	RCT	Humans	CBD (600mg)	Twenty-three healthy participants received a single dose of CBD or placebo	CBD had no significant effect on reward anticipation and feedback

						nor on behavioural measures of motivation for reward
Patra et al., 2020	Preventing premature mortality and improve co-morbidities related to Dravet syndrome	In vitro	Mice	CBD (100 mg/kg twice a day) subcutaneous (SC)	Two models of Dravet syndrome were used to investigate the effects of CBD (100mg/kg b.d) on neonatal welfare and survival and survival and behavioural co-morbidities	Survival was increased by CBD and the worsening of neonatal welfare was delayed. CBD decreased premature mortality and anxiety like and depressive like behaviours and improved social behaviour and memory function

Appendix 6

Anti-inflammatory and anti-oxidant effects of CBD

Study	Effect being studied	Type of study	Subject used	CBD strength	Summary of method	Main findings
Liu et al., 2010	Anti-inflammatory and immuno-modulatory	Animal study	Mice	CBD (1, 5 and 10 mg/kg)	CBD (1, 5 and 10 mg/kg) or vehicle were administered from days 6-10. Ovalbumin was administered 1 hour after the last drug administration, to the footpads of mice to induce delayed type hypersensitivity	CBD (5 and 10mg/kg) demonstrated a decrease in the heavy infiltration of mononuclear cells in the subcutaneous tissues of the footpads. CBD decreased delayed type hypersensitivity reactions. CBD (1, 5, 10 mg/kg) significantly reduced the number of the infiltrated CD3+ and F4/80+ cells in a dose-dependent manner. CBD reduced the expression of the two pro-inflammatory cytokines involved in delayed type hypersensitivity; IFN-γ and TNF-α. CBD (10mg/kg) further produced an anti-inflammatory effect by increasing the number of IL-10+ cells in the footpads (IL-10, is a Th2 associated cytokine possessing anti-inflammatory activity). CBD increased the expression of IFN-γ, a key Th1 cytokine, whereas the Th2 cytokine IL-4 was unaffected
De Filippis et al., 2011	Anti-inflammatory	In vitro	Intestinal biopsies from humans and from mice	CBD (10mg/kg)	Intestinal biopsies from patients with ulcerative colitis (UC) and from intestinal sections of mice with	CBD reduced LPS-induced enteric glial cell activation (specifically S100B expression) in the mouse intestine compared to control group. LPS-treated mice had an increase in mast cell activation and in macrophage activation

					LPS-induced intestinal inflammation were used to investigate the effects of CBD	(specifically MAC-3) which were decreased by CBD treatment. CBD reduced the increased levels of TNF-alpha levels observed in LPS-treated mice. Treatment of LPS-mice with CBD significantly reduced the immunoreactivity for cleaved-caspase 3 (active form of pro-apoptotic enzyme). Pre-administration of UC biopsies with CBD, greatly reduced, in a dose dependant manner LPS and IFN-gamma induced iNOS protein expressions. Additionally, CBD greatly and concentration dependently prevented LPS plus INF-gamma induced nitrite levels (stable metabolite of NO). CBD significantly reduced the expressions of both S100B and iNOS proteins expressed in high levels in un-simulated rectal biopsies. CBD inhibited nitrite production in UC biopsies in acute phase. CBD demonstrates a new therapeutic strategy to treat inflammatory bowel diseases
Kozela et al., 2011	Anti-inflammatory effects in multiple sclerosis like disease	Animal study	Mice	CBD (5mg/kg)	Experimental autoimmune encephalomyelitis (EAE) was induced in mice by myelin oligodendrocyte glycoprotein (MOG).	CBD treatment during the disease onset improved the severity of the clinical signs of EAE. MOG-induced inflammation and axonal damage in the spinal cord and microglial stimulation and T-cell recruitment were all slowed down by CBD. In vitro, CBD treatment

					CBD or vehicle was administered and immunocytochemistry and cell proliferation assays were carried out to assess the effects of CBD	additionally inhibited MOG-induced production of encephalitogenic T-cells
Ruiz-Valdepenas et al., 2011	Anti-inflammatory and antioxidant	Animal study	Mice	CBD (3 mg/kg) intravenously	Mice were induced vascular changes and inflammation. CBD (3mg/kg) was administered	CBD counteracted LPS-induced arteriolar and venular vasodilation and leukocyte margination. The blood brain barrier integrity was preserved with CBD treatment. CBD stopped LPS-induced increases in tumour necrosis factor-alpha and cyclooxygenase-2 expression as measured by quantitative real time PCR. CBD reduced the expression of the inducible-nitric oxide synthase
Karmaus et al., 2012	Effects of CBD on lipopolysaccharide induced pulmonary inflammation	Animal study	Mice	CBD (75 mg/kg) via oral gavage	CBD (75mg/kg) or vehicle was administered to the mice for 3 days. On the last day, approx. one hour before the last dose of CBD, the mice received lipopolysaccharide	CBD significantly increased the levels of inflammatory cells. CBD increased the presence of monocytes, 24 hours after administration of LPS. CBD had no effect on the histology of the lungs but it increased the severity and distribution of LPS-induced pulmonary lesions. At 6 hours after LPS administration, CBD had no effect on LPS-induced pro inflammatory gene expression. But at 24 hours after LPS administration, CBD had increased mRNA

					(LPS) or saline intranasally	expression of TNF alpha, interleukins 6 and 23 and granulocyte colony stimulating factor
Ribeiro et al., 2012	Anti-inflammatory	Animal study	Mice	CBD (0.3, 1.0, 10, 20, 30, 40, and 80 mg/kg) intraperitoneal	Mice were administered CBD prior to the induction of lipopolysaccharide (LPS) induced acute lung injury	CBD doses of 10, 20, 30 and 80mg/kg attenuated TNF production in the bronchoalveolar fluid. This anti-inflammatory effect was dose dependent. CBD (20mg/kg) continuously reduced leukocyte migration into the lungs after the induction of acute lung injury. CBD decreased myeloperoxidase activity 2 and 4 days after induction of inflammation. CBD decreased TNF, IL-6, MCP-1 and MIP-2 concentrations. CBD reduced vascular permeability after the induction of acute lung injury. The anti-inflammatory effects of CBD are decreased by adenosine A2a receptor antagonism
Schicho and Storr, 2012	Anti-inflammatory	Animal study	Mice	CBD 10mg/kg for intraperitoneal treatment CBD 10mg/kg administered via intragastric and intrarectal	Colitis was induced in mice. Individual groups were treated with CBD intraperitoneally (10mg/kg), intragastrically (20 mg/kg) or intrarectally (20 mg/kg). CBD was started one day before	Intraperitoneal injection of 10 mg/kg CBD caused a great improvement of the colitis score index and a reduction in myeloperoxidase activity. Histological sections from lesioned areas also demonstrated less destruction of the epithelial lining, a decrease in colon thickness and less infiltration of immunocytes compared to the control group. Intragastric treatment (CBD 20mg/kg) failed to improve the colitis score. Intrarectal CBD

					induction of colitis and given once daily until the end of the experiments. The effects were monitored by histopathology, macroscopic scoring and myeloperoxidase assay	treatment (20mg/kg), showed a slight improvement in the colitis score index. Myeloperoxidase activity was greatly attenuated indicating a decrease in the severity of the inflammation. Histological sections from lesioned areas in the colon of intrarectally CBD-treated mice showed decreased leukocyte infiltration and partially preserved crypt architecture when compared to the control group
Mecha et al., 2013	Anti-inflammatory effects in TMEV-induced demyelinating disease (TMEV-IDD)	In vivo and in vitro	Mice (in vivo) and rat astrocyte cultures (in vitro)	In vivo - CBD (5 mg/kg) In vitro - CBD (1 or 5 μM)	Sham or TMEV-IDD mice received CBD or vehicle once daily from days 1 to 7 post-infection. Rat astrocyte culture received CBD (1 or 5 μM) or vehicle	CBD decreased VCAM-1 which is part of the immunoglobulin supergene family and reduced chemokine expression in vitro and in vivo. In vivo, CBD inhibited VCAM-1 production and decreased leukocyte adhesion to endothelial cells. Anti-inflammatory effects and long-term immunomodulatory effect produced by CBD were noted in vivo. Adenosine A2a receptors are involved in the CBD-induced reduction of VCAM-1
Yang et al., 2014	Antioxidant, effects on acute alcohol drinking induced steatosis	Animal study	Mice	CBD (5mg/kg) intraperitoneal	Mice were force fed ethanol every 12 hours for 5 days. CBD (5mg/kg) or vehicle were administered 30 minutes before ethanol was given. Serum and	CBD (5mg/kg) every 12 hours prevented an increase in serum aspartate aminotransferase (AST). Ethanol gavage led to a decrease in adenosine triphosphate (ATP), which was reversed by CBD. CBD reduced the increase in hepatic triglycerides which was caused by ethanol and also reduced basal triglycerides

					liver were then collected and analysed	levels. CBD prevented ethanol induced steatosis. CBD attenuated ethanol induced oxidative stress in the livers of the mice who were force fed ethanol. CBD prevented JNK activation by binge ethanol. Treatment of CBD decreased ethanol induced oxidative stress in CYP2E1-expressing HepG2 cells indicating its antioxidant activity. CBD stimulates autophagy in vitro and in vivo which could be another mechanism by which CBD protects the liver from alcohol induced steatosis
Giacoppo et al., 2015a	Effect on encephalomyelitis in MS	Animal study	Mice	CBD cream (1%)	Mice were induced experimental autoimmune encephalomyelitis (EAE). This study consisted of 6 groups: control; EAE group; EAE + CBD; EAE+vehicle; control + CBD and control + vehicle. CBD cream was applied once a day every 24 hours for 28 days starting from EAE induction	CBD treated EAE affected mice demonstrated a lower grade of disability and had a faster recovery time. EAE group + CBD, showed a response to mechanical stimulus. CBD attenuated demyelination and axonal loss in mice induced with EAE. CBD stopped infiltration of inflammatory cells. CBD modulated the production of Treg cells, CD4 and CD8α Tcells. CBD reduces GFAP expression which is a marker for astrogliosis. CBD regulated the inflammatory pathway by increasing IL-10 which is an anti-inflammatory cytokine and by decreasing Il-6, INF-gamma, TGF-beta and TNF-alpha. CBD reduced the production of nitrotyrosine, iNOS and PARP

						and reduced the expression of cleaved-caspase 3. Cleaved- caspase 3 is responsible for programmed cell death.
Hammell et al., 2015	Anti-inflammatory and pain killer	Animal study	Rats	CBD gels (0.6, 3.1, 6.2 or 62.3 mg/day)	A rat complete Freund's adjuvant-induced monoarthritic knee joint model was used to assess the effects of transdermal CBD gel on pain and inflammation. CBD gels (0.6, 3.1, 6.2 or 62.3 mg/day) were applied for 4 days after arthritis induction	Daily applications of 6.2mg and 62.3 mg/day CBD gel for 4 consecutive days significantly reduced the knee joint circumference. Lower doses of CBD had no effect on CFA-induced oedema. 6.2 g/kg of CBD reduced the thickening of the synovial membrane. After 4 days, 6.2mg and 62.3mg/kg significantly improved the pain related to adjuvant –induced monoarthritis. After 2 days of treatment with 6.2 or 62.3 mg/day transdermal CBD, a significant improvement of heat hypersensitivity. CBD did not alter the animals' activity levels or motor abilities. Treatment with high doses of CBD reduced TNFα immunoreactivity which was equivalent to levels of naïve animals. Treatment with high doses of CBD significantly decreased fluorescent intensity of OX42 immunoreactivity to levels below levels in the naive animals. Treatment with high doses of CBD (6.2 and 62.3 mg/day) reduced immunoreactivity to the levels in naïve animals

Kozela et al., 2015	Anti-inflammatory effect in myelin oligodendrocyte glycoprotein (MOG) 35-55-induced mouse	In vitro	Splenocytes co-cultured with MOG35-55-specific T cells (TMOG) and stimulated with MOG35-55	CBD (5 μM)	Splenocytes co-cultured with MOG35-55-specific T cells (TMOG) and stimulated with MOG35-55 received CBD	CBD upregulated T lymphocytes; CD4+ CD25+ CD69 and in LAG3+. This is what exerts its immunoregulatory effects. CBD increased EGR2 mRNA transcription and increased anergy promoting genes such as IL-10 which is an anti-inflammatory cytokine. CBD induced regulatory factors, functional and transcriptional reprogramming of memory T-cells and the decreased activation of B cells
Singer et al., 2015	Antioxidant effects	Animal study	Mice	CBD (0.5, 1.0, 1.5 and 2.5 μM)	Glioma stem cells (GSCs) were used in various assays to assess the response and resistance of GSCs to CBD	CBD induced a robust increase in ROS, which led to the inhibition of cell survival, phosphorylated (p)-AKT, self-renewal and a significant increase in the survival of GSC-bearing mice. Inhibition of self-renewal was mediated by the activation of the p-p38 pathway and downregulation of key stem cell regulators Sox2, Id1 and p-STAT3. CBD upregulated antioxidant response genes and induces a shift to an MES molecular phenotype. CBD treatment with the inhibition of system Xc resulted in synergistic ROS increase leading to robust antitumor effects, that is, decreased GSC survival, self-renewal, and invasion

Vuolo et al., 2015	Anti-inflammatory	Animal study	Mice	CBD (5 mg/kg) intraperitoneal (IP)	Mice were induced asthma. CBD was administered in the last 2 days	The determined serum levels of IL-4, IL-5, IL-13, IL-6, IL-10, and TNF-α were all decreased by CBD treatment except for IL-10 levels
Libro et al., 2016	Anti-inflammation and antiapoptotic	In vitro	Human gingival mesenchymal stem cells (hGMSCs)	CBD (5µM)	hGMSCs were pre-treated with CBD for 24 hours, before transplantation in the host. Gene expression analysis was carried out. This study also consisted or untreated cells and cells treated with vehicle. Both were used as controls.	CBD treatment suppressed genes linked to apoptosis, inflammation and innate immune responses. NOD-liked receptor signalling pathway genes and various pro-inflammatory genes were also suppressed by CBD treatment. Pre-treatment with CBD prevented the stimulation of the NALP3-inflammasome pathway by suppressing the levels of NALP3, CASP1, and IL18 and inhibiting apoptosis via suppression of BAX (a pro-apoptotic mediator). Apoptosis was also suppressed via the downregulation of TNF receptors, initiator caspases and the apoptotic peptidase APAF-1. Stem cell survival was increased due to the upregulation caused by CBD of the transcription of the phosphoinositid-3 kinase (PIK3) subunits and AKT1 serine/threonine kinase 1. CBD modulated the expression of well-known mesenchymal stem cell markers and other surface antigens. CBD treatment led to the downregulation of genes codifying for antigens involved in the stimulation of the immune

						system and to the upregulation of those antigens related to the inhibition of the immune responses
Kozela et al., 2016	Effects on encephalomyelitis model of multiple sclerosis	In vitro	Encephal-itogenic TMOG cells	CBD (5 μM)	Encephalitogenic TMOG cells were stimulated with myelin oligodendrocyte glycoprotein (MOG)35-55 together with spleen-derived antigen presenting cells (APC) with or without CBD	CBD demonstrated a suppression in the transcription of a number of proinflammatory genes (cytokines Xcl1, Il3, Il12a, Il1b, cytokine receptor, transcription factors and TNF superfamily signalling molecules), in TMOG. CBD also had an effect on interleukins. It increased the number of IFN-dependent transcripts which are known to be responsible for their anti-proliferation activity in T cells. CBD increased the transcription of oxidative stress modulators which have a strong anti-inflammatory effect and are controlled by Nfe2l2/Nrf2
Philpott et al., 2017	Anti-inflammatory effects in osteoarthritis	Animal study	Rats	CBD (100, 200, or 300 μg) intra-articular	Osteoarthritis was induced in rats. Two weeks later CBD or vehicle were infused intraarticularly and behavioural pain measurements and inflammation measures were carried out	CBD rapidly reduced noxious movement-evoked firing of knee afferent fibres. 300 μg dose was the most effective one. Low doses of CBD (100 and 200 μg) had no effect on withdrawal threshold or hind limb weight bearing but the 300 μg had greatly increased hind paw withdrawal threshold and hind limb weight bearing. 300 μg of CBD demonstrated a significant reduction in rolling and adherent leukocytes when compared to control. CBD had a moderate inhibitory effect on synovial

						hyperaemia. Anti-rolling and anti-adherence effects of CBD were blocked by receptor antagonists. CBD prophylaxis significantly reduced the development of sodium monoiodoacetate-induced tactile nerve pain during both the acute and late phase of osteoarthritis development. Treatment of CBD during the acute inflammatory phase inhibited saphenous nerve demyelination on day 14 compared to vehicle treated knees but early treatment had no effect on hind limb weight bearing, when compared with vehicle-treated animals
Wang et al., 2017	Anti-inflammatory and antioxidant effects	Animal study	Mice	CBD (5 or 10mg/kg/day)	Chronic plus binge alcohol fed mice and pair-fed mice were used in this study. CBD or vehicle was administered daily throughout the alcohol feeding study and the effects of CBD were monitored	In the chronic plus binge alcohol feeding mice, CBD treatment decreased liver injury and the high levels of serum transaminases ALT and AST. Hepatic lipid/triglyceride accumulation was attenuated by CBD. CBD decreased chronic binge ethanol induced liver inflammation by decreasing alcohol diet-induced increased hepatic mRNA expressions of pro-inflammatory chemokines, monocyte chemotactic protein 1, cytokines, interleukin 1 beta and adhesion molecules selection E. It decreased the hepatic TNFα and SELE levels.

						CBD had no significant effect on these variables in pair-fed mice. CBD decreased liver oxidative/nitrative stress by decreasing the hepatic mRNA expression of reactive oxygen species (ROS). It had no effect on ROS in pair-fed groups. CBD reduced alcohol induced neutrophil accumulation in the liver by decreasing myelopeoridase positive cells. CBD decreased oxidative burst in mouse and human neutrophils independent from cannabinoid 2 receptors. CBD modulated genes and proteins involved in metabolism and liver steatosis by reducing hepatic expression of malonyl-CoA decarboxylase, acetyl-Coenzyme A carboxylase alpha, increasing gene expression involved in fatty acid oxidation
Callejas et al., 2018	Anti-inflammatory	Animal study	Pregnant rat model	CBD (30mg/kg)	Gastroschisis (GS) was induced in pregnant rat models and CBD was administered 3 days after. Foetuses were divided into four different groups. The foetuses were harvested and	The body weight in the group consisting of CBD and induced GS was lower than the control plus CBD. Intestinal weight and intestinal weight with body weight ratio was lower in the group with CBD and GS compared to the group with only GS. CBD and GS presented with lower thickness in all parameters compared to the group with GS and inflammation and nitrite/nitrate levels were lower in the group that had GS and CBD. Maternal use of CBD had a

					evaluated for various levels and analysis	beneficial effect on the intestinal loops of GS. CBD of experimental GS in rats reduced the weight, thickness of intestinal layers, concentration of NO2/NO3, and expression of iNOS of the bowel loops showing an effective anti-inflammatory action and pharmacological application for pre-natal use
Elliott et al., 2018	Anti-inflammation in multiple sclerosis (MS)	In vivo and in vitro	Mice	CBD (20mg/kg) intraperitoneal (IP)	Experimental autoimmune encephalomyelitis (EAE) was induced in mice. CBD 20mg/kg or vehicle was given on day 9 till day 5 I.P. The effects of CBD were also investigated in vitro using myeloid-derived suppressor cells (MDSCs)	CBD reduced EAE disease as seen from the great reduction in clinical scores of paralysis, lower T cell infiltration in the central nervous system and reduced levels of IFN-gamma and interleukin-17. CBD stimulated anti-inflammatory cytokines (IL-17) and transcription factors while attenuating pro-inflammatory cytokines (IL-10). CBD resulted in a great increase in MDSCs in EAE mice in contrary to vehicle treated MDSCs. A lot of inhibition of myelin oligodendrocyte glycoprotein-induced production of T cells in vitro was caused by MDSCs. The decrease of EAE by CBD treatment can be reversed with MDSC depletion
Li et al., 2018	Anti-inflammatory	Animal study	Mice	CBD (1.5mg/kg) intraperitoneal (IP)	Female mice were exposed to spinal cord contusion injury (SCI). CBD or vehicle	In the group that had SCI and CBD, a decrease in pro-inflammatory cytokines, interleukins and chemokines associated with T-cell differentiation and invasion was noticed.

					was administered for 10 weeks after injury	CBD treated mice did not develop moderate to severe thermal sensitivity unlike the group that was administered the vehicle. CBD did not affect recovery of locomotion or bladder function following SCI. CBD mitigated the development of thermal sensitivity following spinal cord injury
Gegotek et al., 2019	Antioxidant and anti-inflammatory effects	In vitro	2D and 3D cultured skin fibroblasts models	CBD (4 µM)	Human skin fibroblasts were irradiated with UVA and UVB then incubated for 24 hours in a medium containing CBD	In the 2D cultured cells, following UVA/UVB radiation, changes associated with proteins involved in antioxidant response and inflammation were noted. In the 3D cultured fibroblasts, following UVA/UVB radiation, the changes noted were mainly related with the stimulation of signalling pathways
Jastrząb et al., 2019	Anti-inflammatory and antioxidant effects on the expression of keratinocytes	In vitro	Human keratinocytes	CBD (0, 0.1, 0.5, 1, 2, 4, 10, 25, 50, 100 nmoles/mL)	Human keratinocytes underwent UV radiation followed by incubation for 24 hours, in a medium containing 0, 0.1, 0.5, 1, 2, 4, 10, 25, 50, 100 nmoles/mL CBD	CBD in UV irradiated keratinocytes, greatly increased the effects of antioxidant enzymes such as superoxide dismutase and thioredoxin reductase. CBD prevented lipid peroxidation which was characterised by reduced levels of 4-HNE and 15d-PGJ2. CBD's antioxidant activity and anti-inflammatory activity were observed via Nrf2 activation and NFκB inhibition, respectively
Muthumalage and Rahman, 2019	Anti-oxidant, anti-inflammatory	In vitro	Epithelial cells, lung fibroblast	CBD (10.6, 21.2, 42.4 µM)	Epithelial cells, macrophages and lung fibroblast cells were	CBD showed differential pro- and anti-inflammatory effects by ROS levels. CBD significantly attenuated LPS-induced NF-κB

			cells and macrophages		treated with varying CBD concentrations or exposed to CBD. Monocytes and epithelial cells were stimulated with LPS in combination with CBD or dexamethasone to understand the anti-inflammatory effects of CBD	activity and IL-8 and MCP-1. CBD and dexamethasone reduced the IL-8 level induced by LPS. CBD has a differential inflammatory response and acts as an antagonist with steroids. Cytotoxicity caused by the highest concentration of CBD (42.4 μM)
Casares et al., 2020	Anti-oxidant	In vivo and in vitro	Mice (in vivo) and primary human keratinocytes (in vitro)	CBD (10 μM) CBD cream (0.1-1%)	Primary human keratinocytes were cultured in keratinocyte growth medium with or without CBD (10 μM) for 24 hours. Mice were treated with CBD based creams to assess the effects of CBD on the skin.	CBD is involved in keratinocyte differentiation, skin development and epidermal cell differentiation. CBD activated the transcriptional activity of NRF2 which is an important transcription factor in keratinocyte biology. CBD upregulated heme oxygenase 1 (HMOX1). BACH1 is a molecular target for CBD in keratinocytes. The effect of BACH1 on HMOX1 expression is not dependent on NRF2. In vivo, topical CBD increased wound repair and the production and levels of HMOX1
Jarocka-Karpowicz et al., 2020	Antioxidant, anti-inflammatory	In vitro	Keratinocytes of psoriatic or	CBD (4 μM)	Keratinocytes isolated from psoriatic or healthy patients	Redox imbalance in UV-irradiated keratinocytes of healthy participants was reduced by CBD by attenuating reactive oxygen

			healthy patients		underwent UVA and UVB irradiation. CBD treatment followed	species (ROS), increasing vitamin A and E levels and increasing the Thioredoxin-dependent system efficiency. However, CBD increased the oxidative and inflammatory state in the keratinocytes of psoriatic participants following UV irradiation
Atalay et al., 2020	Anti-oxidant, Anti-inflammatory	Animal study	Rats	CBD (2.5g)	CBD was applied to the back of the animal every 12 hours for 4 weeks and then it was removed. Every 48 hours before CBD application, the skin of the back was exposed to UVA or UVB every 48 hours for 4 weeks. Five groups – control, UVA exposure, UVA plus CBD exposure, UVB exposure, UVB plus CBD exposure	CBD helped normalise the expression of keratinocyte proteins that are metabolically relevant by modelling their biosynthesis and degradation. It maintained the proteostasis of keratinocytes. CBD prevented UV-mediated activation of proteins. CBD prevented protein degradation and stimulated protein biosynthesis. It promoted an increase of a central antioxidant enzyme. CBD modified the structure of the nuclear inhibitor Nrf2 - BACH1 and contributed to the protection of cells against harmful environmental factors

Appendix 7

CBD effects on neurological conditions

Study	Effect being studied	Type of study	Subject used	CBD strength	Summary of method	Main findings
Avraham et al., 2011	Neuro-protection and liver protection in hepatic failure	Animal study	Mice	CBD (5 mg/kg) intraperitoneal (IP)	Mice were administered saline or thioacetamide and treated either with a vehicle or CBD. Neurological and motor functions were evaluated. Hepatic failure was induced and histopathological analysis and blood analysis were carried out	CBD demonstrated an improved neurological score in thioacetamide treated mice compared to thioacetamide alone. CBD significantly increased the activity level and improved cognitive function in thioacetamide treated mice compare to untreated mice. Thioacetamide increased the whole brain's 5-HT levels. These were partially restored by CBD. Administration of thioacetamide increased the number of activated astrocytes which were greatly reduced by CBD. There was no difference in cellular size or extension of processes between CBD and vehicle-treated thioacetamide mice. CBD reversed the increased levels of ammonia, bilirubin, aspartate transaminase and alanine transaminase, in the plasma, caused by thioacetamide. CBD did not have affect the neurological score, activity, cognitive function and levels of 5-HT in control animals
Jones et al., 2012	Effect on seizures	Animal study	Rats	CBD (1, 10 5, 100 or 200mg/ kg)	Wistar rats were used in the seizure and rotarod test models. CBD (1, 10 or	In the pilocarpine model, CBD greatly decreased the percentage of rats experiencing the most severe seizures. In the penicillin model, CBD (doses equal or greater than 10mg/kg) reduced

					100mg/kg) was administered before any seizure experiments while CBD (50, 100 or 200mg/kg) was administered before any motor function tests	the percentage mortality as a result of seizures. All doses of CBD attenuated the percentage rats experiencing the most sever tonic-clonic seizures
Gomes et al., 2013	Effects on catalepsy	Animal study	Mice	CBD (5, 15, 30 or 60mg/kg) intraperitoneal (IP)	Mice were pre-treated with CBD (5, 15, 30 or 60mg/kg) 30 minutes before administering haloperidol, L-nitro-N-arginine (L-NOARG) or WIN55,212-2 (a CB1 receptor agonist). The mice were tested at different times after being administered either one or the other. CBD (30mg/kg) was administered 30 minutes later	CBD (30 and 60mg/kg) decreased the cataleptic effects of haloperidol 2 hours after administration but not at 1 hour and 4 hours. CBD (30 and 60 mg/kg) reduced the cataleptic effect of L-NOARG 1, 2 and 4 h after injection while CBD (15mg/kg) reduced the effect after 1 and 2 hours after injection. CBD (15, 30, and 60mg/kg) decreased catalepsy induced by WIN55,212-2 1 and 2 hours after injection. CBD did not induce catalepsy and neither did WAY100635. WAY100635 was able to block the anticataleptic effects of CBD demonstrating that CBD reduces catalepsy induced by various drugs through facilitation of 5-HT1A receptor-mediated neurotransmission

Hess et al., 2016	Antiepileptic effects in drug resistant epilepsy in tuberous sclerosis complex (TSC)	Clinical trial	Humans	CBD (5mg/kg/day, max dose 50mg/kg/day)	Eighteen patients with TSC received CBD for 3 months. The initial dose was 5mg/kg/day with weekly increments of 5mg/kg. Max dose was 50mg/kg/day	CBD caused a reduction in the frequency of all seizure types, which was experienced by all the patients. The responder rate after 3 months was that of 50%. Cognitive gains and behavioural improvements were noted
Peres et al., 2016	Effects on cognitive impairment	Animal study	Rats	CBD (0.5 or 5mg/kg)	Rats were administered CBD (0.5 or 5mg/kg) or vehicle on day 2-5. The same rats were administered reserpine or vehicle on days 3 and 5	CBD was unable to reduce the decrease in locomotion caused by reserpine however CBD reduced the catalepsy, the motor and cognitive impairments and the vacuous chewing movements caused by reserpine
Devinsky et al., 2017	Anti-epileptic effects	RCT	Humans	CBD oral solution (20mg/kg/day)	One hundred and twenty children and adolescents with Dravet syndrome (DS) were administered CBD or placebo in addition to their anti-epileptic medication. The frequency of seizures was	Convulsive seizures per month was reduced by CBD from 12.4 to 5.9 seizures when compared to placebo. The percentage of patients who experienced more or less a 50% reduction in convulsive seizure frequency was 43% with CBD and 27% with placebo. CBD improved the patient's overall condition by at least one category on the seven-category Caregiver Global Impression of Change scale (62%). CBD attenuated the frequency of total seizures but

					monitored over a 14-week period	there was no significant decrease in nonconvulsive seizures. Five percent of the patients who were administered CBD became seizure free
Do Val-da Silva et al., 2017	Behavioural, electrophysiological and neuropathological effects of CBD in epilepsy	Animal study	Rats	CBD (10mg/kg) intraperitoneal (IP)	CBD was administered before pilocarpine induced status epilepticus (SE) or before and after SE	CBD decreased the behavioural severity and oscillatory electrographic changes of SE. CBD decreased post-ictal lethargy and the neuronal loss related to pilocarpine induced SE. CBD decreased neurodegeneration in the SE + CBD group
Kaplan et al., 2017	Antiepileptic effects in Dravet syndrome	Animal study	Mice	CBD (10, 20, 100 or 200mg/kg) I.P and CBD (10, 16 μM)	A mouse genetic model of Dravet syndrome (DS) underwent various tests to investigate the effects of CBD on seizures and social deficits	CBD (100 and 200mg/kg) protected DS mice against febrile and spontaneous seizures. CBD (100mg/kg) reversed the hyperactivity of DS mice. Low doses of CBD (10 or 20mg/kg) rapidly reversed the autistic like behavioural deficit. CBD (10mg/kg) increased the number of social interactions and reduced the number of defensive escapes. CBD indirectly decreased excitatory transmission and directly augmented GABAA receptor-mediated inhibition. It decreased excitatory output from the dentate gyrus and increased inhibitory neurotransmission through the blockade of GPR55

Álvarez Bravo et al., 2018	Antiepileptic effects in Dravet syndrome	Case report	Human	CBD (no mention)	A 19-year-old patient with a history of treatment resistant epilepsy received CBD as an adjunct to her antiepileptic treatments	CBD reduced the number of seizures and also improved motor abilities
Devinsky et al., 2018b	Antiepileptic effects in Lennox-Gastaut syndrome	RCT	Humans	CBD (10 or 20mg/kg)	Two-hundred and twenty-five participants with Lennox-Gastaut syndrome received 10mg/kg or 20mg/kg CBD or placebo twice daily for 14 weeks	CBD reduced the frequency of drop seizures, with the 20mg/kg having a higher percent reduction (41.9% in the 20mg/kg and 37.2% in 10mg/kg CBD)
Devinsky et al., 2018c	Antiepileptic effects in severe childhood epilepsy	Clinical trial	Humans	CBD (Epidiolex®) (2.5mg/kg/day twice daily titrating to 25mg/kg/day, maximum dose of 50mg/kg/day)	Fifty children and young adolescents with severe childhood onset of epilepsy were administered CBD (Epidiolex®) for 48 weeks	CBD decreased the monthly convulsive seizure frequency in all patients. The percent change in monthly convulsive seizure frequency in those patients taking CBD was reduced from baseline
Devinsky et al., 2018a	Anti-epileptic effects in	Clinical trial	Humans	CBD (Epidiolex®)	Two-hundred and sixty-four patients	During weeks 1-12, CBD decreased the monthly frequency of seizures by 37.5%. This reduction

	Dravet syndrome			(2.5 to 20 mg/kg/day, maximum 30mg/kg/day)	with Dravet syndrome (DS) received Epidiolex® for 48 weeks	was sustained until the end of the study. 4.8% of the patients were seizure free during the last 12 weeks of CBD treatment. 85% of the participants or their caregivers reported an over improvement in their condition after 48 weeks of CBD treatment
Khan et al., 2018	Anti-epileptic effects of CBD in status epilepticus (SE)	In vivo and in vitro	Rats (in vivo) and hippo-campal brain slice model (in vitro)	CBD (100mg /kg) (in vivo) and CBD (5, 8 and 10 μM) (in vitro)	Two seizure models were used, in vivo kainic acid (KA)-induced epilepsy and an in vitro Mg2+-free hippocampal brain slice model. For neuroanatomical studies, rats were randomly assigned to one of the four groups: control, epileptic vehicle, CBD given at time zero and CBD given 20 mins after SE	CBD reduced seizure activity by reducing excitation at pyramidal cells by decreasing the amplitude of excitatory postsynaptic potential (EPSPs). CBD did not greatly change the EPSP rise time or the duration at either membrane potentials. CBD exerted a cell type-specific alteration of membrane properties of CA1 neurons. After bath-application of 10 mcgM CBD, significant changes in the intrinsic membrane properties were noted. CBD enhanced inhibitory synaptic potentials elicited by fast spiking and adapting interneurons at postsynaptic pyramidal cells. Pyramidal cell's hyperactive membrane properties were restored by CBD. CBD reduced intrinsic excitability of cholecystokinin (CCK) adapting interneurons in CA1. CBD enhanced excitability of FS-PV interneurons in the CA1 region of the hippocampus. CBD significantly attenuated the density of PV- and CCK- expressing neurons in

						epileptic rats when compared to the control group. It restored the morphological pathology of PV- and CCK- expressing interneurons
Maggio et al., 2018	CBD effects on behavioural seizure activity	Animal study	Mice	CBD (30mg/kg) intraperitoneal (IP)	Status epilepticus was induced in the mice by using pilocarpine. CBD was administered 45 minutes before seizure induction	Long term potentiation (LTP) in pilocarpine treated mice was restored by CBD. CBD administered to naïve mice caused an increase in LTP production. CBD counteracted the effect of seizure-producing pilocarpine on LTP generation
Szaflarski et al., 2018	Anti-epileptic effects of CBD in drug resistant epilepsies	Clinical trial	Humans	CBD (Epidiolex®) (5mg/kg/day to 50mg/kg/day)	Seventy-two children and 60 adults with treatment resistant epilepsy were administered CBD starting from 5mg/kg/day and increasing up to 50mg/kg/day for 48 weeks	The average dose was between 20 and 30mg/kg/day. CBD greatly improved adverse events profile and severity and frequency of seizures at 12 weeks up until the duration of treatment
Gu et al., 2019	Effects of CBD in Angelman syndrome	Animal study	Mice	CBD (100mg/kg)	Angelman syndrome model was used. CBD (100mg/kg) was administered acutely and for 2 weeks	CBD reduced the severity and frequency of seizures triggered by acoustic stimuli and decreased the severity and frequency of hyperthermia-induced generalised seizures. However, acute and chronic treatment of CBD

						did not halt the proepileptogenic plasticity shown in AS model
Thiele et al., 2019	Anti-epileptic effects of CBD in Lennox-Gastaut (LGS)	RCT	Humans	CBD (Epidiolex®) (2.5 to 20 mg/kg/day, maximum 30mg/kg/day)	Three-hundred and thirty-six patients with LGS were invited to enrol in this interim analysis where patients received Epidiolex® starting from 2.5mg/kg/day titrating up to 20mg/kg/day over 2 weeks	A continuous decrease in total and drop seizures was observed through the whole 48 weeks. Throughout the 48 weeks, less than 4% of the patients experienced episodes of either convulsive or nonconvulsive status epilepticus. Eighty-eight percent of patients/caregivers noted improvement in overall condition after 48 weeks of CBD treatment
Anderson et al., 2020	Effect of CBD in refractory epilepsy	Clinical trial	Humans	CBD (Epidiolex® 5mg/kg/day twice a day in divided doses. Dose was increased by 5mg/kg every 1-2 weeks)	Patients underwent an electroencephalogram at the start of the study then underwent another one after being on CBD treatment for a month and then after 12 months	CBD decreased seizure frequency. CBD had an effect on brain network dynamics which is important for the treatment of refractory epilepsy
Gray et al., 2020	Anti-convulsive activity of CBD	Animal study	Mice	CBD (10, 25,50, 100 mg/kg)	Transient receptor potential vanilloid 1 (TRPV1) knockout and wildtype mice	Significant increase in seizure threshold was detected in the wildtype mice treated with 50 and 100mg/kg CBD when compared to the vehicle groups. There was a significant increase in

					were randomly given a vehicle or CBD, 1 hour before delivering and electroshock. Diazepam was used as a positive control	seizure threshold in TRPV1 knockout mice with CBD only at 100mg/kg compared to the vehicle group. Wildtype mice treated with 50 mg/kg CBD had significantly increased seizure threshold compared with TRPV1 knockout mice at the same dose and were not significantly different from TRPV1 knockout mice treated with 100 mg/kg CBD
Koo et al., 2020	Anti-epileptic effects of CBD in Lennox-Gastaut (LGS) and Dravet syndrome (DS)	Clinical trial	Humans	CBD (initiated at 5mg/kg/day and maintained at 10mg/kg/day)	Patients with LGS or DS received Epidiolex®. The frequency of seizures experienced per month was evaluated	52.9% of the patients with LGS experienced a decreased in seizure frequency at 3 months and 29.4% of the patients experienced it at 6 months. Eight patients were seizure free at 3 months. No significant changes in EEG activity were observed after the administration of CBD. With regards to the patients with DS, 1 patient was seizure free, 2 patients demonstrated a reduction of more than 50% in seizure frequency and 60% of the patients had no effects
D'Onofrio et al., 2020	Anti-epileptic effects of CBD in drug resistant epilepsies; Lennox-Gastaut (LGS) and Dravet	Clinical trial	Humans	CBD (Epidiolex®) (2.5mg/kg/day to 10mg/kg/day after 4 weeks with a maximum dose	One hundred and twenty-five participants were administered CBD. Efficacy was analysed at month 1, 2 and 6 while comparing the two sets of subgroups;	CBD reduced the frequency of monthly seizures by ≥50% (in 28 patients), by ≥70% (in 23 patients) and by ≥90% (in 6 patients). These were experienced at month 6. One patient was seizure free after one month of treatment and two patients (1 DS and 1 LGS) were seizure free after 6 months. The decrease in seizure did not differ greatly between the two sets of subgroups

	syndrome (DS)			of 20mg/kg/day)	LGS against DS and patient with clobazam against patients without	

Appendix 8

Anti-tumour, antiangiogenic and apoptotic effects of CBD

Study	Effect being studied	Type of study	Subject used	CBD strength	Summary of method	Main findings
McAllister et al., 2011	Anti-tumour effects on breast cancer	In vitro and in vivo	Human breast cancer cells (in vitro) and mice (in vivo)	In vitro - CBD (1.5 μM) In vivo – CBD (1 or 5mg/kg)	Western analysis, cell proliferation and invasion assays, cell flow cytometry were used to investigate the effects of CBD on breast cancer cells. Mice were used to investigate whether CBD reduces metastasis in vivo	CBD up regulated ERK phosphorylation and Id-2 expression and extracellular signal-regulated kinase phosphorylation. It inhibited Id-1 expression and corresponding human breast cancer cell proliferation and invasiveness through ERK. This inhibition is decreased by α-tocopherol (TOC) which is a ROS scavenger. Down regulation of Id-1 expression, proliferation, and invasion in mouse metastatic breast cancer cells was observed by CBD. In vivo, CBD attenuated primary tumour growth and greatly decreased metastasis in immune competent mouse models of breast cancer
Shrivastava et al., 2011	Cell death in breast cancer	In vitro	Human cell lines	CBD (0–10 mmol/L)	Human cell lines were pre-treated with multiple drugs and apoptosis was quantified using fluorescein isothiocyanate. CBD was then administered with	CBD attenuated cell viability of both oestrogen receptor positive and negative cell lines in a concentration dependent manner. CBD induced apoptosis in breast cancer cell lines in a receptor independent manner. CBD treated cells showed apoptosis and autophagy. It mediated autophagy and apoptosis by inducing

					increasing concentrations for 24 hours	endoplasmic reticulum in breast cancer cells and stopping AKT/mTOR/4EBP1 signalling which is an important oncogenic pathway. CBD caused apoptosis in breast cancer cell lines through the mitochondria mediated signalling pathway. CBD required ROS generation and beclinl for its apoptosis and autophagy effects
Maor et al., 2012	Effect on cell death in Kaposi Sarcoma – Associated Herpesvirus (KSHV) infected endothelium	In vitro	KSHV infected tissue samples and primary adult human microvascular endothelial cells (HMVEC)	CBD (0.1, 1, 5, 10 μM)	Human endothelial cells and human endothelial cells infected with Kaposi Sarcoma were incubated with various concentrations of CBD	CBD did not modulate the infection of human endothelial cells by KSHV. KSHV infected HMVEC compared to normal HMVECs exhibited a reduced in proliferation and experienced cell death which was induced by CBD. CBD downregulated the expression of KSHV viral G protein coupled receptor (vGPCR), the chemokine growth regulated protein alpha (GRO-α), vascular endothelial growth factor receptor 3 (VEGFR-3), its ligand and growth factor (VEGF-C)
Solinas et al., 2012	Anti-angiogenic properties	In vitro and in vivo	Human umbilical vein endothelial	CBD (2.5, 5.0, 7.5, 10.0, 12.5, 15.0, 17.5, 20.0 μM)	HUVECs were exposed to CBD at different concentrations and the	In vitro, HUVEC production and migration was inhibited by CBD. CBD did not cause an induction of toxicity nor apoptosis in HUVECs. The expression

			cell (HUVEC) (in vitro) and mice (in vivo)		angiogenesis effect of CBD was investigated	pattern of angiogenesis-related proteins in HUVECs were modified by CBD. CBD prevented endothelial morphogenesis and the outgrowth of capillary-like structures from HUVEC spheroids. In vivo, angiogenesis was inhibited by CBD. All these effects were linked to the down regulation of many angiogenesis-related molecules
Solinas et al., 2013	Antitumour effects on human glioma cell lines	In vitro	Human glioma cell lines U87-MG and T98G	CBD (0.5, 1, 5, 9, 12 μM)	CBD was administered to human glioma cell lines; U87-MG and T98G	Proliferation and invasiveness of human glioma cell lines U87-MG and T98G were inhibited by CBD. The expression of proteins involved in tumour development, invasion and angiogenesis in glioma cells were attenuated by CBD. CBD downregulated ERK and Akt prosurvival signalling and hypoxia inducible factor HIF-1a expression
Elbaz et al., 2015	Anti-tumour effects on breast cancer	In vitro and in vivo	Human and murine triple negative breast cancer cells (in vitro) and mice models (in vivo)	In vitro – CBD (3, 6, 9, 12, 15 μM) In vivo – CBD (10mg/kg)	Tumour was induced in the mice models and CBD 10mg/kg or vehicle was administered for 3 weeks. The tumours were measured on a weekly basis.	In vitro, CBD greatly inhibited the formation, migration and invasion of triple negative breast cancer cells (TNBC) stimulated by epidermal growth factor (EGF). CBD modulated EGF and EGFR which are the signalling pathways needed to activate cellular targets that are vital for cancer cell survival, migration

						and invasion. This modulation is through inhibition of the stimulation of EGFR, AKT, ERK and NF-kB signalling plus the blockage of MMP's secretion and the suppression of phalloidin expression and actin stress fibre formation. In vivo, CBD prevented tumour growth in the mice models by suppressing tumour cell formation, angiogenic potential and inhibiting the stimulation of EGFR, AKT and ERK proteins. Metastasis of breast cancer cells to the lung were inhibited by CBD through reduced MMP2 and MMP9 secretion by the tumour cells. CBD inhibited tumour growth and metastasis through inhibition of macrophage recruitment to tumour sites
Giacoppo et al., 2015b	Antiapoptotic in multiple sclerosis	Animal study	Mice	CBD (10 mg/kg) intraperitoneal (IP)	Experimental autoimmune encephalomyelitis (EAE) was induced in the mice. On the 14th day, the EAE group and control group received CBD (10mg/kg) IP	EAE group treated with CBD demonstrated a quicker improvement in general wellness. The EAE treated group which was not treated with CBD led to a constant loss of paw sensibility. CBD prevented Fas pathway activation, phospho-ERK p42/44 and cleaved caspase-3 triggering and also alterations

						in mitochondrial permeability due to Bax/Bcl-2 unbalance. This confirms CBD's anti-apoptotic effects. CBD interfered with p53-p21 axis activation and with the formation of neuronal apo bodies
Gigli et al., 2017	Anti-apoptotic, mucosal protection	In vitro	Caco-2 cells	CBD at 10^{-9}, 10^{-8} and 10^{-7} M	Caco-2 cells were exposed to Clostridium difficile toxin A (30 ng/ml) with or without CBD, in the presence of the specific antagonist AM251 (10−7 M)	Effects of Clostridium difficile toxin A were significantly and concentration-dependently counteracted by CBD. The antagonist AM251 stopped the effect of CBD on the Clostridium difficile toxin A induced transepithelial electrical resistance reduction. 10−7 M CBD showed to restore epithelial barrier architecture and function. CBD inhibited apoptosis and cells' toxicity. The protective effects of CBD are mediated by CB-1 receptor
Kalenderoglou et al., 2017	Antitumour effects on human leukemic cell line	In vitro	Jurkat T cell line (lymphoblastic disease model)	CBD (0.01-10 μM)	Human leukemic cell line Jurkat were treated with CBD for 24 hours and then a total of another 72 hours after the treatment	At concentrations greater than 1 μM, CBD inhibited cell viability. At a dose of 10 μM, CBD inhibited cellular respiration. Cell cycle was delayed by CBD. CBD deactivated the mTOR pathway and decreased cell size. Normal physiological levels of oxygen rendered cells resistant to CBD which concludes

						that CBD might not be clinically useful as an anticancer treatment
Da Silva et al., 2018	Antiapoptotic effects	Animal study	Rats	CBD (10mg/kg)	Adult rats were administered vehicle or iron carbonyl on day 12 and 14 postnatal, followed by the treatment of vehicle or CBD for 14 days.	CBD reversed the iron-induced effects and recovered apoptotic proteins such as caspase 9, and 3, APAF1 and cleaved PARP. These results indicate that CBD has neuroprotective effects via its anti-apoptotic action
Alharris et al., 2019	Apoptotic effect	In vitro	Human neuroblastoma cell lines	CBD (5 or 10 μM)	CBD was administered in human neuroblastoma cell lines	Apoptosis was induced by CBD via the activation of serotonin and vanilloid receptors. Caspase-2 and -3 were also involved. NBL cell migration and invasion was greatly decreased by CBD. Mitochondrial respiration was inhibited by CBD which led to a glycolysis. CBD caused changes in miRNA which led to promote cell death
Jeong et al., 2019	Anti-tumour, apoptosis	In vitro and in vivo	Human gastric carcinoma AGS, MKN45, and MKN74 cells (in vitro) and xenograft	In vitro – CBD (4 μM) In vivo – CBD (20mg/kg) subcutaneously	Human gastric carcinoma AGS, MKN45, and MKN74 cells were treated with CBD and the effects were assessed. Xenograft mouse model was administered CBD (20mg/kg) SC and tumour growth was monitored.	In vitro, CBD promoted apoptosis in gastric cancer by downregulating X-linked inhibitor apoptosis (XIAP) via the ubiquitin-proteasome system. SMAC levels, which is an inhibitor of XIAP, were increased during CBD treatment. CBD led to mitochondrial dysfunction and increased the relation between XIAP

			mouse model (in vivo)			and SMAC by increasing the release of SMAC from mitochondria to the cytosol. In vivo, CBD prevented tumour growth in the mice
Winklmayr et al., 2019	CBD effects in osteoarthritis	In vitro	Human articular chondrocytes and human immortalised C28/I2 cells	CBD (1 nM to 10 μM)	Human articular chondrocytes and C28/I2 cells were incubated with various concentrations of CBD for 5 hours.	CBD decreased cell viability and induced apoptosis in human articular chondrocytes. CBD produced a cytotoxic effect above 5 μM. Doses below 10 μM did not affect cell viability. CBD increased intracellular calcium in C28/I2 and in human chondrocytes. This influx of extracellular calcium induced apoptosis and is partially mediated through CB1 receptors. CBD induced an increased in phosphorylation of ERK1/2 which is not mediated by CB1 receptor
Zhang et al., 2019	Anti-tumour, apoptosis	In vitro	Human gastric cancer SGC-7901 cells	CBD (5, 10, 20, 30, and 40 μg/mL)	Human gastric cancer SGC-7901 cells were treated with CBD (5, 10, 20, 30, and 40 μg/mL)	CBD (5–40 μg/mL) treatment inhibited the production and colony formation of human gastric cancer cells. An upregulation in ataxia telangiectasia-mutated gene (ATM) and p53 protein expression was caused by CBD. CBD downregulated p21 protein expression in human gastric cells which led to the inhibition of CDK2 and cyclin E levels causing cell cycle arrest at the G0–G1

						phase. BAX levels were increased, Bcl-2 expression levels and mitochondrial membrane potential were decreased and cleaved caspase-3 and cleaved caspase-9 were upregulated by CBD resulting in the induction of apoptosis. CBD treatment caused an increase in reactive oxygen species (ROS) at intracellular level
Łuczaj et al., 2020	Apoptotic effects in skin conditions	In vitro	Psoriatic keratinocytes and healthy keratinocytes	CBD (4µM)	This study consisted of 8 groups of keratinocytes; Control; healthy cells + CBD; healthy cells + UVB; healthy cells + UVB +CBD; psoriatic patients (Ps); Ps+ CBD; Ps + UVB and Ps +CBD +UVB. Psoriatic and healthy keratinocytes were cultured in a medium containing CBD (4µM) for 24 hours.	Phospholipids; phosphatidylcholine (PC), phosphatidylinositol (PI), phosphatidylserine (PS) and phosphoethanolamine (PEO) were decreased in psoriatic keratinocytes while sphingomyelin (SM) was increased. CBD in psoriatic keratinocytes led to a further reduction in PC and PS but an increase in PEO and SM. The exposure of UVB-irradiated cells to CBD attenuated the level of SM. CBD prevented the loss of trans epidermal water of keratinocytes exposed to UVB

Appendix 9

Cardioprotective effects of CBD

Study	Effect being studied	Type of study	Subject used	CBD strength	Summary of method	Main findings
Rajesh et al., 2010	Cardio-protective	Animal study	Mice and primary human cardiomyocytes	CBD (1, 10 or 20 mg/kg) intraperitoneal (IP)	One-week diabetic mice were treated with vehicle or CBD (1, 10 or 20 mg/kg) for 11 weeks. Eight-weeks diabetic mice were treated with CBD or vehicle for 4 weeks	CBD reduced myocardial dysfunction, cardiac fibrosis, inflammation, oxidative and nitrosative stress, cell death and interrelated signalling pathways. The high glucose induced increased ROS generation, NF-κB activation and cell death in primary human cardiomyocytes were also decreased by CBD
Walsh et al., 2010	Cardio-protective and anti-arrhythmic	Animal study	Rats	CBD (10 or 50 mg/kg) intravenously (IV)	Rats were administered vehicle or CBD (10 or 50 mg/kg) 10 minutes prior to 30 minutes coronary artery occlusion or CBD (50 mg/kg) 10 minutes prior to reperfusion	CBD demonstrated a reduction in the total number of ischaemia-induced ventricular arrhythmias and in infarct size when administered prior to ischaemia. When CBD was given before reperfusion, infarct size was attenuated. CBD (50 mg/kg) reduced collaged induced platelet aggregation before ischaemia not at reperfusion. A single dose of CBD is enough to reduce myocardial tissue injury irrelevant if it is given before or after coronary occlusion

Granjeiro et al., 2011	Cardio-protective effects	Animal study	Rats	CBD (15, 30 and 60 nmol) intracisternal	Rats underwent a stereotaxic surgery and were then randomly assigned to one of the treatment groups	During exposure to restraint stress, CBD (15 and 60 nmol) did not induce any significant change on heart rate and mean arterial pressure. CBD (30 nmol) reduced cardiovascular responses to restraint stress. CBD (30nmol) decreased the percentage of entries onto the open arms of the elevated plus-maze. CBD can decrease autonomic responses to stress. CBD decreased the anxiogenic consequences of restraint stress
Ali et al., 2015	CBD effects on contractility and its electrophysio logical properties	In vitro	Rat ventricular myocytes	CBD (1 µM)	Video edge detection, Calcium sensitive fluorescent indicator fura-2 AM, whole cell path clamp and radioligand binding methods were used on the rat ventricular myocytes	CBD caused a significant reduction in the amplitudes of electrically-evoked myocyte shortening and calcium 2+ transients and inhibited L-type calcium2+ channels. CBD decreased myocyte contractility by suppressing L-type Ca2+ channels at a site different than dihydropyridine binding site and inhibits excitation-contraction coupling in cardiomyocytes
Hao et al., 2015	Anti-oxidant, anti-inflammatory and	Animal study	Mice	CBD (10 mg/kg) intraperitoneal	Mice were treated with CBD 10 mg/kg IP, or vehicle started 1.5 h	CBD reduced myocardial oxidative stress, tissues injury and cardiac dysfunction and increased ejection fraction and fractional shortening.

	prevention of DOX-induced cardiopathy				before the DOX injection and once every day	CBD reduced myocardial cell death and myocardial inflammation by decreasing myocardial expression of mRNAs of tumour necrosis factor-α (TNFA), interleukin-1β (IL1B) and monocyte chemoattractant protein-1 (MCP-1). CBD enhanced mitochondrial biogenesis in damaged hearts
Lee et al., 2016	Effects of CBD on myocardial inflammation, dysfunction and remodelling	Animal study	Mice	CBD (10mg/kg) intraperitoneal (IP)	A mice model of experimental autoimmune myocarditis (EAM) was used. The mice were divided into four groups – control treated with vehicle, EMA treated with vehicle, EMA treated with CBD and Freund's complete adjuvant (CFA) treated with vehicle. Mice were either treated with CBD or vehicle on a daily basis	CBD reduces inflammation in EAM myocardium by attenuating the inflammatory cell invasion and necrosis. CBD reduced gene expression levels of T-cell markers, monocytes and dendritic cell marker and macrophage marker in the left ventricular of EAM mice. CBD reduced mRNA expression of the proinflammatory cytokines specifically IL-6, IL1β and IFN-γ and had the tendency to reduce the mRNA levels of MCP1. CBD reduced inflammation associated oxidative stress markers in EAM by reducing the mRNA expression of p47phox and by reversing the downregulation of

						sarco/endoplasmic reticulum ATPase2a2 (SERCA). CBD significantly reduced 3- Nitrotyrosine (3-NT) and 4-Hydroxynonenal (4-HNE) content in the left ventricular of EAM animals. CBD protected against fibrotic remodelling of the myocardium in EAM. CBD improved systolic function and left ventricular myocardium contractility and reversed the EAM-related diastolic dysfunction and myocardial stiffness
Jadoon et al., 2017	Cardio-protective effects	RCT	Humans	CBD (600mg)	CBD (600mg) or placebo was given to 9 healthy participants	During stress tests, particularly the cold tests, CBD reduced systolic and diastolic blood pressure and stroke volume. Cardiac output was maintained and heart rate was increased
Wheal et al., 2017	Cardio-protective effects	Animal study	Rats	CBD (10mg/kg) intraperitoneal (IP)	CBD or vehicle was administered to Zucker Diabetic fatty (ZDF) rats or ZDF lean rats for 7 days	In ZDF rats, CBD enhanced vasorelaxation in mesenteric arteries. This was not observed in ZDF lean rats. CBD improved serum biomarkers such as serum C-peptide and insulin
Kossakowski et al., 2019	Anti-hypertensive	In vivo and in vitro	Rats (in vivo) and atria isolated	CBD (1, 3, 10 and 30mg/kg)	Cardiovascular effects of CBD in spontaneously hypertensive (SHR) and	In pithed SHR and WKY rats, CBD 1, 3, and 10 mg/kg given to the same rat

			from the rats (in vitro)	intravenously (IV)	normotensive Wistar Kyoto (WKY) rats were examined. Experiments were carried out on conscious, urethane-anesthetized and pithed rats.	increased heart rate (HR) and systolic blood pressure (SBP) and decreased diastolic BP (DBP) in a manner insensitive to adrenalectomy. In anesthetized rats, bolus IV injection of single doses of CBD (3, 10 and 30mg/kg) caused dose-dependent reductions in HR, SBP, and DBP. These effects were stronger in SHR than in WKY. Bilateral vagotomy prevented or strongly diminished the cardiovascular responses to CBD (10 mg/kg). CBD reduced the Bezold-Jarisch reflex elicited by the 5-HT3 receptor agonist phenyl biguanide but not that evoked by the TRPV1 agonist capsaicin. In conscious rats, CBD did not affect cardiovascular parameters. In isolated left atria, CBD decreased contractile force
Baranowska-Kuczko et al., 2020	Anti-hypertensive, vasodilatory effects	In vitro	Human pulmonary arteries and small mesenteric arteries	CBD (10mmol/l)	Isolated human pulmonary arteries obtained from patients during resection of lung carcinoma and small mesenteric arteries	CBD produced a concentration-dependent and endothelium-dependent relaxation of human pulmonary arteries. CBD produced a time-dependent slowly developing decrease in the tone of endothelium-intact

					isolated from spontaneously hypertensive; 11-deoxycorticosterone acetate hypertensive rats or their appropriate normotensive controls were used to examine vascular effects of CBD	human pulmonary arteries. CBD's vasorelaxant effects were decreased by comorbidities
Sadowska et al., 2020	Anti-hypertensive effects on Monocrotaline (MCT)-induced pulmonary hypertension rats	Animal study	Rats	CBD (10mg/kg/day)	MCT-induced pulmonary hypertension rats were administered CBD 10mg/kg/day for three weeks	CBD reduced pulmonary hypertension in RVSP and improved oxygen saturation. There were no modifications related to lung weight to BW ratio. There were no effects in the control group. CBD reduced the pulmonary artery medial wall thickness in the MCT-treated rats. There was no effect in the control group. CBD administration in MCT-treated rats completely restored (when compared to control groups) the efficacy of both vasorelaxants and potency of sodium nitroprusside but not acetylcholine. No changes in control groups. MCT reduced the levels of palmitoleoyl ethanolamide,

						N-arachidonoyl glycine, eicosapentenoyl ethanolamide, linolenoyl ethanolamide and anandamide. Chronic CBD increased these levels in lungs of MCT-treated rats. MCT treated rats had an increase in plasma PAI-1, tissue plasminogen activator levels and white blood cell count all of which were reduced by CBD administration

Appendix 10

Other therapeutic effects of CBD

Study	Effect being studied	Type of study	Subject used	CBD strength	Summary of method	Main findings
Rock et al., 2012	Anti-emetic and anti-nausea	In vivo and in vitro	Musk shrews and rats (in vivo) Cell membranes from rat brainstem (in vitro)	CBD (2, 4, 5, or 10mg/kg) intracranial and systemic	Rats were used to investigate the anti-nauseas like effects of CBD while musk shrews were used to investigate the anti-emetic effects of CBD. 5-HT1a receptor antagonists were administered to prevent the potential effects of CBD. Nicotine, Lithium Chloride or cisplatin were used to induce vomiting. Lithium chloride induced gaping was carried out using rats. Rat brainstem membranes were used to investigate the potential of CBD to directly target specific receptors	CBD suppressed nicotine, lithium chloride and cisplatin (20mg/kg but not 40mg/kg) induced vomiting in shrews and suppressed the lithium chloride induced conditioned gaping in rats. These effects were reversed by the 5-HT1a receptor antagonists. When CBD was administered to the dorsal raphe nucleus (DRN), it produced anti-nausea like effects which were reversed by systemic administration of 5-HT1a receptor antagonists. CBD increased the ability of a 5-HT1a receptor agonist to stimulate [35S] GTP gamma S binding to rat brainstem membranes. Systematic administration of CBD and 8-OH-DPAT synergistically suppressed lithium chloride-induced conditioned gaping. These results suggest that CBD produced its anti-emetic/anti-nausea effects by indirect activation of the somatodendritic 5-HT1A auto receptors in the DRN

Silveira et al., 2014	Effects of CBD on lesion-induced intervertebral disc degeneration	Animal study	Rats	CBD (30, 60 or 120nmol) intradiscal injection	Intervertebral disc injury was induced in rats using a single needle gauge needle. CBD (30, 50 or 120nmol) was injected intradiscally exactly after the disc injury induction. MRI and histological analyses were carried out to investigate the effects	Low doses of CBD (30 and 60 nmol) did not affect MRI pixel intensity but CBD 120nmol greatly improved MRI pixel intensity two days after administration. Fifteen days after the lesion induction and administration of CBD 120nmol, MRI examination was carried out again and then histological analyses were carried out as well. The effect of CBD 120nmol was still observed. Histological changes were observed with CBD 120nmol. CBD (120nmol) significantly reduced the effects of disc injury induced by the needle puncture
Stanley et al., 2015	Vascular effects of CBD	In vitro	Human mesenteric arteries	CBD (0.1-100 μM/L)	Human mesenteric arteries were collected from patients undergoing colorectal surgery. CBD was administered to these human mesenteric arteries	CBD produced an acute, non-recoverable vasorelaxation of the human mesenteric arteries, which is mediated via CB1 receptors, potassium channel stimulation, TRP channels and the endothelium. NFkB, p70s6 K, phosphorylated JNK and STAT5 were greatly decreased by CBD while Akt levels, ERK1/2, eNOS and phosphorylated CREB were greatly increased by CBD

Yeshurun et al., 2015	Prevention of graft-versus-host-disease (GVHD) after transplantation	Clinical trial	Humans	CBD (150mg)	All 48 transplant patients received the standard GVHD prophylaxis. CBD 150mg was administered twice a day 7 days before transplantation until day 30	During treatment with CBD no patient developed acute GVHD. After discontinuation of CBD, one patient developed grade I acute GVHD and 7 other patients developed grade II to IV GVHD
Toyang et al., 2017	Effects in viral hepatitis	In vitro	Hepatitis cells	CBD (10 µM)	HepG2 2.2.15 and Huh7.5 cells were used to culture viral hepatitis B and C respectively. CBD (10 µM) was administered as a single dose	CBD demonstrated antiviral activity against hepatitis C but not hepatitis B, yet it still demonstrated significant cytotoxicity against HepG2 2.2.15 cells. CBD had a direct antiviral activity against hepatitis C
Baban et al., 2018	Immunoregulatory and renoprotective effects	Animal study	Mice	CBD (10mg/kg)	The impact of CBD treatment on regulatory T-17 cells and neutrophil polarisation in mice subjected to bilateral renal ischaemia-reperfusion injury was studied. Then the kidneys underwent flow cytometry analyses	CBD treatment caused significant renoprotective effects accompanied by a decrease in the phenotypes N1 and Th-17 cells and an increase in the development of regulatory/suppressive phenotypes of neutrophils (i.e., N2) and T cells (i.e., Treg17 cells). CBD treatment decreased the total neutrophils in the kidneys of the animals subjected to ischaemia-reperfusion injury. CBD treatment also affected neutrophil polarisation. CBD significantly supressed T cell proliferation. CBD reduced kidney cell

						death, increased renal perfusion and reduced creatinine
Palmieri et al., 2019	Effect on chronic skin conditions	Clinical trial	Humans	CBD ointment	Twenty patients with a history of skin conditions were instructed to apply topical CBD- ointment to the affected areas twice a day for three months	CBD improved skin hydration, elasticity and trans epidermal water loss in various parts of the body. A reduction in papules and pustules was noted. An improvement in the severity of psoriasis was also noted
Salles et al., 2020	Effect on acute respiratory distress syndrome	Animal study	Mice	CBD (5mg/kg) intraperitoneal	Mice were split into 3 groups: control, Poly (I:C) and Poly (I:C) plus CBD. Mice were administered a synthetic viral dsRNA (Poly (I:C)) intranasally for 3 days to mimic the symptoms of acute respiratory distress syndrome (ARDS). CBD was administered 2 hours after the second injection of Poly (I:C) and then every other day for a total of 3 doses	Poly (I:C) treated mice experienced decreased levels of T cells, increased neutrophils and a great reduction in the expression level of Apelin, which is a substrate for ACE2. These effects were reversed by CBD. CBD stopped perivascular and peri-bronchiolar interstitial inflammatory infiltrate, hypertrophy, fibrosis and pulmonary oedema which were caused following administration of Poly (I:C)

Appendix 11

CBD effects on different types of pain

Study	Effect being studied	Type of study	Subject used	CBD strength	Summary of method	Main findings
Ward et al., 2011	Effects on allodynia induced by paclitaxel	Animal study	Mice	CBD (5.0 or 10.0 mg/kg) intraperitoneal (IP)	Mice and CBD treated mice were administered paclitaxel or saline. Non-CBD treated mice were administered paclitaxel or saline on days 1, 3, 5 and 7 while CBD treated mice were administered once daily on days 1 to 14	Paclitaxel induced allodynia in the mice, both cold and mechanical allodynia. CBD (5 and 10mg/kg) prevented the development of cold and mechanical allodynia induced by paclitaxel
Ward et al., 2014	Pathways through which CBD effects on neuropathic pain induced by paclitaxel are exhibited	Animal study	Mice	CBD (2.5 – 10 mg/kg) intraperitoneal (IP)	Female mice were pre-treated with CBD or vehicle before paclitaxel treatment	CBD protected against paclitaxel induced neurotoxicity and mechanical sensitivity was prevented. The effects of CBD were reversed by a 5-HT1A antagonist. CBD did not have an effect on the activity and efficacy of paclitaxel in inhibiting breast cancer cell viability
Genaro et al., 2017	Analgesic effects of CBD on mechanical allodynia and on incision pain	Animal study	Rats	CBD (0.3 to 30mg/kg) intraperitoneal (IP) or intracerebral	Rats were succumbed to a model of incision pain. All rats had mechanical allodynia. Vehicle injections or CBD injections were given to the	CBD attenuated mechanical allodynia at 3 and 10mg/kg doses. CBD (1 mg/kg) induced significant conditioned place preference (CPP) in injured rats. CBD injections into the rACC decreased mechanical nerve

					rats, IP or into the rostral anterior cingulate cortex (rACC).	pain in incised rats and induced CPP. CBD (1 and 3 mg/kg) reversed the CPP delivered by peripheral nerve block. CBD evoked similar antinociceptive effects via rACC and via the systemic route
De Gregorio et al., 2019	Effect of CBD on the firing activity 5-HT neurons in the dorsal raphe nucleus	Animal study	Rats	CBD (0.1-1.0 mg/kg) intravenous IV CBD (5mg/kg) subcutaneous (SC)	Rats were administered increasing doses of CBD (0.1-1.0 mg/kg) IV. Rats were treated with repeated treatment of CBD (5mg/kg) SC. Rats were subjected to spared nerve injury model for 24 days	Acute administration of CBD decreased firing activity of dorsal raphe nucleus 5-HT neurons through 5-HT1a and TRPV1 receptors. Continuous treatment with CBD increased firing effects of dorsal raphe nucleus 5-HT neurons via the desensitisation of 5-HT1a receptors. Paw withdrawal threshold was increased with repeated treatment of CBD after spared nerve injury surgery and spared nerve injury–induced deficits and anxiety-like behaviour were reversed by CBD. Low doses of CBD induced analgesia through TRPV1 activation, reduced anxiety through 5-HT1A receptor activation, and rescued impaired 5-HT neurotransmission under neuropathic pain conditions

Nitecka-Buchta et al., 2019	Myorelaxant and antinociceptive effects on temporomandibular disorders (TMD)	RCT	Humans	20% CBD oil	Eighty-seven patients who were temporomandibular disorder–positive, were administered placebo or transdermal CBD twice a day for 14 days	In the CBD treated group, there was a significant reduction (24%) in the masseter muscle activity compared to the control group. The pain intensity in the visual analogue scale (VAS) was greatly attenuated in 70% of the CBD treated group. The condition of masticatory muscles in patients with myofascial pain was improved with CBD
Anand et al., 2020	Nociceptor desensitization and therapeutic effect of CBD	In vitro	Cultured rat sensory neurons	CBD (1, 10, 100 nMol/L and 1, 10, 50 μMol/L)	Cultured adult rat dorsal root ganglion (DRG) neurons were supplemented with neurotrophic factors. Neurons were activated with CBD at various concentrations. Separate experiments were also carried out using capsaicin instead with or without CBD	At CBD doses of 10 and 50 μMol/L, DRG neurons showed calcium influx. DRG neurons treated with capsaicin showed vigorous calcium influx, which was dose-dependently decreased in the presence of low dose CBD (100 nMol/L). The increased availability of cAMP led to phosphorylation and sensitisation of TRPV1 which were prevented by CBD. CBD attenuated the levels of cAMP and inhibited TRPV1 signalling

Appendix 12

Neuroprotective effects of CBD

Study	Effect being studied	Type of study	Subject used	CBD strength	Summary of method	Main findings
Liput et al., 2013	Neuroprotective effects in alcohol induced neurodegeneration	Animal study	Rats	CBD transdermal gel (1.0%, 2.5% and 5.0%) CBD (40mg/kg/day) intraperitoneal (IP)	The neuroprotective effects and target of transdermal CBD for the treatment of alcohol induced neurodegeneration were assessed by conducting two experiments	In experiment 1, CBD gels were evaluated for neuroprotection. 5% CBD gel resulted in a reduction in neurodegeneration in the entorhinal cortex. Experiment 2 compared 2.5% transdermal gel and intraperitoneally CBD. Both showed similar magnitudes of neuroprotection. Both reduced Fluoro-Jade B positive cells in the entorhinal cortex
Santos et al., 2015	Neuroprotective effects in 1 -methyl-4-phenylpyridinium iodide (MPP+) induced toxicity	In vitro	PC12 and SH-SY5Y cells	CBD (1, 5, 10, 25, 50 μM)	PC12 and SH-SY5Y cells were given MPP+ to induce toxicity. CBD was administered	CBD increased cell viability, reduced the activity of caspase-3 and induced cellular differentiation in MPP+ treated PC12 cell lines. CBD also protected against the downregulation of cellular differentiation produced by MPP+. CBD increased the expression of synaptophysin, synapsin I and GAP-43 in MPP+-treated PC12 cells. The neurorestorative effects of CBD are independent of nerve growth factor (NGF)
Hind et al., 2016	Effect on blood brain barrier (BBB) following ischaemia	In vitro	Human brain microvascular endothelial cell (HBMEC)	CBD (1, 10, 100 μM)	Human brain microvascular endothelial cell (HBMEC) and human astrocyte co-cultures	Four hours of OGD caused an increase in permeability which was prevented by CBD (10 μM). CBD was most effective when administered prior to OGD. Protective effects were noted 2 hours into reperfusion.

			and human astrocyte co-cultures		received CBD treatment (1, 10, 100 μM) and its effects on BBB permeability was assessed. Ischaemia was presented by oxygen–glucose deprivation (OGD)	CBD attenuated cell damage and CBD attenuated VCAM-1 and increased VEGF levels in HBMEC monocultures
Sun et al., 2017	Neuroprotective effects of CBD in an oxygen-glucose deprived/reperfusion model	In vitro	Mouse hippocampal neuronal cell line	CBD (1, 2.5, 5, 10 μM)	CBD was supplemented in an oxygen-glucose-deprivation/reperfusion (OGD/R) model.	CBD supplementation during reperfusion protects the hippocampal cells against OGD/R induced cytotoxicity. It maintained the normal appearance of cells and reduced the morphological damage. CBD decreases OGD/R-induced cell death in hippocampal neurons and attenuates OGD/R induced oxidative stress in hippocampal neurons. This was demonstrated from the decreased effects in MDA and ROS levels, increased effects in reduced glutathione levels and increase in glutathione peroxidase and SOD1 activities. CBD improved mitochondrial bioenergetics and regulated glucose metabolism in OGD/R injured neurons. Pentose-phosphate pathway of glucose metabolism in OGD/R-injured

						hippocampal neurons were improved by CBD
Da Silva et al., 2018	Neuroprotective effects in iron-induced neurodegeneration	Animal study	Rats	CBD (10mg/kg) intraperitoneal	Rats were administered iron during their neonatal period and CBD for 14 days during adulthood	CBD restored hippocampal epigenetic modulation of mtDNA. CBD increased mitochondrial ferritin levels which may be related to its neuroprotective effects. CBD rescued succinate dehydrogenase activity in iron treated rats

Appendix 13

List of publications and abstracts

Abstracts submitted for the 80th FIP World Congress of Pharmacy and Pharmaceutical Sciences 2022, Seville.

Accepted for poster presentations.

Therapeutic Potential of Cannabidiol

Abigail Calleja

Janis Vella Szijj, Anthony Serracino-Inglott

Background: Cannabidiol (CBD) is one of the most prevalent phytocannabinoids found in the cannabis plant. CBD and tetrahydrocannabinol (THC) have a similar chemical structure though they differ in the spatial configuration which leads to differences in their pharmacological profiles. There is a growing interest about the promising pharmacological properties of CBD.

Purpose: To investigate the potential therapeutic benefits of CBD in different medical conditions.

Method: Systematic literature review about studies on potential therapeutic benefits of CBD was carried out. PubMed® was used to retrieve peer reviewed open access and full text articles from January 2010 till December 2020. Publications that were neither experimental studies nor observational studies and studies with ongoing results or no results were excluded. Publications describing approved or potential therapeutic effects of CBD used alone in different medical conditions were included. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses style method was employed. The impact factor of the journals containing the studies was identified.

Results: A total of 2,637 articles were identified, of which 126 articles met the inclusion criteria for review. CBD was reported to have beneficial effects on mental health disorders (33), inflammatory conditions (27), neurological disorders (21), tumours (15), cardiovascular disease (11) and neuropathic pain (6). CBD demonstrated neuroprotective effects (5) and other therapeutic effects (8). Fifty-five of the 126 studies were '*in vivo*' studies, 33 were human studies, 23 were '*in vitro*' and 15 were '*in vitro and in vivo*' studies. The journals including the studies which demonstrated that CBD has an effect on neurological conditions had the highest average impact factor:14.39. The 21 studies reporting the effect of CBD on neurological conditions demonstrated that CBD reduced the frequency and severity of seizures and improved cognitive and motor abilities and behaviour.

Conclusion: Results gathered from the systematic literature search support that CBD has recognised therapeutic effects and has promising pharmacological purpose. CBD is a naturally occurring compound derived from cannabis that has beneficial and therapeutic effects and also adverse effects. Further human studies investigating the therapeutic effects need to be carried out on a wider scale with carefully structured clinical trials.

Cannabidiol: knowledge and perceptions of society

Abigail Calleja

Janis Vella Szijj, Anthony Serracino-Inglott

Background: Cannabidiol (CBD) and tetrahydrocannabinol (THC) are cannabinoids found in the cannabis plant. Research and marketing efforts about the use of CBD increased the public's interest and knowledge about its use.

Purpose: To assess the knowledge and perception of the general public about CBD.

Method: A questionnaire targeting the knowledge and perception of the general public about CBD was developed, validated and disseminated. Ethics approval was granted. The questionnaire consisted of 4 sections: Demographics, Knowledge, Perception and Barriers related to CBD use.

Results: Four hundred individuals (62% female, 41% aged 26-40 years, 42% having a tertiary level of education) answered the questionnaire. Seventy five percent of respondents from the general public (n=257) learned about CBD from social media/news and 88% (n=247) of the participants discussed the use and effects of CBD with friends/family. Ninety six percent (n=384) agree that CBD has a therapeutic effect with 79% (n=314) believing that CBD has an analgesic effect and 76% (n=305) believing that CBD has an anxiolytic effect. Forty-five percent (n=180) believe that CBD causes sedation and drowsiness, 3.8% (n=15) do not know if CBD has any side effects and 8% (n=32) believe that CBD has no side effects. Fifty percent (n=202) of the participants are of the opinion that CBD products should be prescription-only-medicine and 69% (n=277) disagree that CBD is a gateway drug. Eighty-five percent (n=342) of the participants believe that CBD products should be accessible in Malta for medicinal use and 77% (n=306) agree that CBD products recommended or prescribed by a healthcare

professional are more likely to be used by patients. Fifty-three percent (n=210) of the participants agree with the statement that use of CBD might lead to judgemental issues or conflicts between healthcare professionals. Participants who were knowledgeable about CBD (67.9%) believe that 'Social stigma associated with use of CBD for medicinal use would be a potential barrier related to CBD use). Participants who are not knowledgeable about CBD (53.8%) perceive 'Risk of impaired driving' and 'Misuse of CBD products' as potential barriers related to CBD use.

Conclusion: The findings demonstrate that participants were aware and knowledgeable about CBD. The majority of the participants (n=314) believe that CBD has an analgesic effect, yet there is no approved CBD medicinal product indicated for painful conditions on the market. Findings demonstrate that there are participants who do not know whether CBD has any side effects or believe that it has none, indicating lack of knowledge among the public with regards to the side effects caused by CBD. Results indicate that CBD products recommended or prescribed by a healthcare professional are more likely to be used by patients.

Reflections on the use of Cannabidiol for Medicinal Purposes and the views of Healthcare Professionals

Abigail Calleja

Janis Vella Szijj, Anthony Serracino-Inglott

Background: The cannabis plant has more than one hundred cannabinoids. The two most researched cannabinoids are tetrahydrocannabinol (THC) and cannabidiol (CBD). Demand for CBD products grew with healthcare professionals recommending CBD for potential therapeutic effects.

Purpose: To assess the knowledge and perception of healthcare professionals (HCPs) about CBD.

Method: A questionnaire targeting the knowledge and perceptions of HCPs about CBD was developed, validated and disseminated to medical doctors, pharmacists, nurses, podiatrists and other HCPs. Ethics approval was granted. The questionnaire consisted of 4 sections: Demographics, Knowledge, Perception and Barriers related to CBD use.

Results: One hundred fifty HCPs58% female, 53% aged 26-40 years, 49% pharmacists, 23% medical doctors, 8% nurses, 7% podiatrists, 5% psychologists) answered the questionnaire. Seventy percent (n=97) of HCPs obtained information about CBD from social media/news, 61% (n=91) had patients asking them about CBD and its use and 69% (n=104) feel comfortable in prescribing or recommending CBD for pain. HCPs (n=105) believe that sedation/somnolence are from common to very common side effects caused by CBD while fever (n=90), infections (n=80) and drooling (n=59) were believed to be rare to very rare side effects of CBD. Fifteen percent (n=22) were aware about Epidiolex® / Epidyolex®, 60% (n=90) believe that Epidyolex® should be available in Malta and 53% (n=79) believe that CBD products intended for medicinal use without a marketing

authorization should not be legally available in Malta. Sixty-seven percent (n=101) of HCPs believe that CBD products should be prescription-only medicines where 39% (n=58) are of the opinion that CBD products should be prescribed following the same procedure for controlled and dangerous substances. Sixty-one percent (n=91) disagree that CBD is a gateway drug, 45% (n=67) agree that CBD products used for recreational purposes should be decriminalised and 65% (n=97) of HCPs deemed their personal beliefs as a barrier to CBD use.

Conclusion: The majority (n=145) of the HCPs claim that CBD produces an analgesic effect yet there is no approved CBD product for the management of pain. HCPs (n=58) believe that CBD products should be considered as narcotics. Sedation and somnolence were believed to be from common to very common side effects caused by CBD. Drooling, fever and infections were believed to be rare to very rare side effects of CBD. These results indicate different levels of knowledge among HCPs. The side effects mentioned in the questionnaire were listed as common to very common side effects in the SmPC of Epidiolex® / Epidyolex®. Awareness and education about the potential side effects caused by CBD products is proposed.