UNIVERSITY OF
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# THE EFFECTS OF CBD-DOMINANT LIGHT CANNABIS IN HUMANS: THE ROLE OF CBD IN THE SUBJECTIVE, COGNITIVE, AND PSYCHOLOGICAL EFFECTS OF LOW-THC CANNABIS WITH A HIGH CBD TO THC RATIO

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# Abstract

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Kylliäinen, Antti: The effects of CBD-dominant light cannabis in humans: The role of CBD in the subjective, cognitive, and psychological effects of low-THC cannabis with a high CBD to THC ratio

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**Keywords: cannabis, cannabidiol, tetrahydrocannabinol, cannabinoids, mixture effects**

Cannabis is the most popular illegal drug of abuse worldwide and the recent movement towards liberalization has led to development of a sizeable market for cannabis products. Industrial hemp is a type of cannabis plant with low tetrahydrocannabinol- or THC concentration, and it is typically regulated separately from high-THC drug-type cannabis so many low-THC cannabis products including light cannabis are derived from it. The genetic basis of cannabinoid biosynthesis favors relatively high cannabidiol or CBD content in many cannabis plants that are cultivated for industrial use and CBD-dominant light cannabis products have been particularly prevalent in the European Union member states, including Finland.

THC in cannabis produces acute subjective effects, cognitive impairment and psychological symptoms, but it has been reported that these are notably mild or absent in the users of light cannabis. CBD has been suggested to modulate THC effects and even ameliorate the adverse effects of THC so the high CBD content of light cannabis could play a role by mitigating the THC effects. CBD could therefore alter the hazard characteristics of THC incorporated into cannabinoid mixtures with high CBD:THC ratios that are found in light cannabis products as well. The aim of this study was to characterize the composition of cannabinoid mixtures found in light cannabis based on the existing literature and then determine the role of CBD in modulating the effects of THC in similar mixtures by conducting a systematic review of literature.

The systematic review revealed that interventional studies in humans, comparing the acute effects of THC alone and in mixtures with CBD, have administered cannabinoids almost exclusively in mixture ratios that did not correspond well to, and were lower than, those characterized typical for light cannabis. At these lower mixture ratios, CBD did not produce clinically significant modulation of THC acute effects. Findings of the systematic review do not suggest that CBD-dominant light cannabis should be considered differently from drug-type cannabis in risk assessments based on high CBD-content or CBD:THC ratio alone.

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**Avainsanat: kannabis, tetrahydrokannabinoli, kannabidioli, seosten vaikutukset**

Kannabis on jo kauan ollut maailmanlaajuisesti käytetyin huumausaine ja lisäksi viime aikoina useissa maissa on siirrytty kohti sallivampaa ilmapiiriä sekä päihdepolitiikkaa, minkä vuoksi kannabistuotteista on tullut kaupallisesti varsin merkittäviä. Teollisuushamppu on kannabiskasvi, jonka tetrahydrokannabinoli- eli THC pitoisuus on matala ja jota tyypillisesti koskee erillinen sääntely kuin korkeita THC-pitoisuuksia sisältävää, huumausaineeksi luokiteltavaa, kannabista. Teollisuushamppua käytetäänkin useiden matalan THC-pitoisuuden kannabistuotteiden, mukaan lukien kevytkannabiksen, raaka-aineena. Kannabinoidien biosynteesin geneettinen perusta suosii verrattain korkeita kannabidioli- eli CBD-pitoisuuksia useissa teollisuuskäyttöön risteytetyissä kannabislajikkeissa ja CBD-dominantteja kevytkannabistuotteita onkin tavattu yleisesti markkinoilla useissa Euroopan unionin jäsenvaltioissa, mukaan lukien Suomessa.

Kannabiksen THC aiheuttaa akuutisti subjektiivisia vaikutuksia, kognitiivisen suorituskyvyn laskua ja psykologisia oireita, mutta näitä ei tyypillisesti ole tavattu kevytkannabiksen käytön yhteydessä lainkaan tai ne ovat olleet huomattavan lieviä. CBD:n on ehdotettu moduloivan THC:n vaikutuksia ja jopa lievittävän THC:n haitallisia vaikutuksia, joten on mahdollista, että kevytkannabikselle tyypillinen verrattain korkea CBD-pitoisuus voisi merkittävästi lieventää siinä esiintyvän THC:n vaikutuksia. CBD voisi siten muuttaa THC:n vaaraa aiheuttavia ominaisuuksia, kun yhdisteet esiintyvät seoksina, joiden CBD:THC suhde on korkea ja jollaisia on tavattu myös kevytkannabistuotteista. Tämän tutkimuksen tarkoitus oli karakterisoida kevytkannabiksen sisältämien kannabinoidiseosten koostumus aiempaan kirjallisuuteen pohjautuen ja sitten määrittää systemaattisen kirjallisuuskatsauksen keinoin, millainen rooli CBD:lla on THC:n vaikutusten moduloijana tällaisissa seoksissa.

Katsauksessa selvisi, että Ihmisillä suoritetuissa kokeellisissa interventiotutkimuksissa, joissa on vertailtu puhtaana ja CBD-seoksissa annosteltujen THC-annosten vaikutuksia, on annosteltu lähestulkoon yksinomaan seoksia, joiden CBD:THC suhdeluvut ovat kevytkannabista huomattavasti alhaisempia. Annostelluissa seossuhteissa CBD:n ei ole havaittu moduloivan THC:n akuutteja vaikutuksia kliinisesti merkitsevällä tavalla. Kirjallisuuskatsauksen löydökset eivät puolla kevytkannabiksen päihdekannabiksesta poikkeavaa huomiointia riskinarvioinneissa pelkästään korkeampaan CBD-pitoisuuteen tai CBD:THC suhteeseen perustuen.

# Abbreviations (1/2)

| | |
|---|---|
| 2-AG | 2-Arachidonoyl glycerol |
| 5-HT1A | Serotonin 1A receptor |
| 11-OH-THC | 11-hydroxy-tetrahydrocannabinol metabolite |
| Δ8-THC | Δ8-Tetrahydrocannabinol. |
| AEA | Arachidonoyl ethanolamide, Anandamide |
| ARCI | Addiction Research Center Inventory |
| BPRS | Brief Psychiatric Rating Scale |
| CADSS | Clinician Administered Dissociative States Scale |
| CB1/CB2 | Cannabinoid Receptor 1/Cannabinoid receptor 2 |
| CBC | Cannabichromene |
| CBC-A | Cannabichromenic acid |
| CBD | Cannabidiol |
| CBD-A | Cannabidiolic acid |
| CBG | Cannabigerol |
| CBG-A | Cannabigerolic acid |
| CBN | Cannabinol |
| CEQ | Cannabis Experiences Questionnaire |
| CNS | Central Nervous System |
| CUD | Cannabis Use Disorder |
| EMCDDA | European Monitoring Centre for Drugs and Drug Addiction |
| EWL | Adjective Mood Rating Scale (Eigenschaftswörterliste) |
| FAAH | Fatty acid amide hydrolase |
| GC-MS | Gas chromatography – mass spectrometry |
| HHC | Hexahydrocannabinol |
| MAGL | Monoacyl glycerol lipase |

## Abbreviations (2/2)

| | |
|---|---|
| MDMA | 3,4-Methylenedioxymethamphetamine, ecstasy |
| MRF | Marijuana Rating Form |
| MS | Mass spectrometry |
| NHLBI | National Heart, Lung, and Blood Institute |
| PANSS | Positive and Negative Syndrome Scale |
| PICO | Population, Intervention, Comparator, Outcome |
| PRISMA | Preferred Reporting Items for Systematic review and Meta-Analysis |
| PSI | Psychotomimetic States Inventory |
| SSC | Semi-synthetic cannabinoid |
| STAI | State Trait Anxiety Inventory |
| THC | Δ9-Tetrahydrocannabinol, Tetrahydrocannabinol |
| THC-A | Tetrahydrocannabinolic acid |
| THCV | Tetrahydrocannabivarin |
| THL | Finnish Institute for Health and Welfare, Terveyden ja hyvinvoinnin laitos |
| TRPV | Transient receptor potential vanilloid (receptor channels) |
| UHPLC | Ultra-High-Performance Liquid Chromatography |
| VAS | Visual analogue scales |

# Contents

# 1 Introduction

Cannabis is the most common drug of abuse in Finland and according to surveys by THL its use has steadily increased over the past decades (Karjalainen et al. 2013). The same surveys reveal a change towards more relaxed attitudes and risk perception related to the use of cannabis. It is reasonable to predict that these trends are continuing in the future, as generational analysis of user cohorts aligns with a sustained increasing trend (Hakkarainen et al. 2020) and the global trends towards cannabis liberalization are likely to affect the attitude of younger generations of potential future users. Despite the relatively benign nature of cannabis as a drug of abuse compared to many other substances, including alcohol and tobacco (Amsterdam et al. 2015), cannabis can still cause serious harm to users who adopt dangerous patterns of use. Cannabis is therefore an increasingly relevant health concern both in Finland as well as the rest of the world.

Cannabis as a drug of abuse is mostly criticized over its negative cognitive and psychological effects that are strongly associated with Δ9-tetrahydrocannabinol, or THC, a psychoactive and intoxicating compound present in the cannabis plant - *Cannabis sativa*. Furthermore, it seems that higher THC concentrations cause an increase in the prevalence and severity of cannabis related health harm (Curran et al. 2016). It is therefore troubling that over the past decades the average THC levels of available cannabis has been increasing, thus leading to an increased risk associated with cannabis use (Chandra et al. 2019). Eventually, these combined trends of expanding user base and increasing potency could lead to a substantial rise in the prevalence of cannabis related cognitive harm and psychiatric disorders.

Industrial hemp is a variety of Cannabis sativa with low THC content that is for practical reasons considered separately from the narcotic drug-type cannabis in various legislative frameworks in both the United States and in the European Union and is not subject to similar control and restrictions as high-THC cannabis (Hughes 2018). Recently, a market for products derived from industrial hemp, that resemble products derived from regular drug-type cannabis, has appeared and since then expanded rapidly. A colloquial term has been coined for these consumable industrial hemp products and they are thus called “light cannabis” in media and some scientific literature, but according to the European Monitoring Centre for Drugs and Drug Addiction

(EMCDDA) these are also known as “low-THC cannabis products” (Hughes et al. 2020). A significant marketing point for light cannabis has been cannabidiol or CBD, a psychoactive, but non-intoxicating cannabinoid that purportedly has many health benefits such as anxiolytic and antipsychotic properties but so far has only been approved as medication for rare intractable epilepsies and has very complex pharmacological interactions with THC (Huestis et al. 2019).

Drug-type cannabis has high average THC content and often very high THC to CBD ratio (THC:CBD), or relative difference in concentrations of THC and CBD. By contrast, light cannabis has been reported by multiple studies to have a variable but low THC content of less than one percent, and almost invariably a very high CBD to THC ratio (CBD:THC) (Marchei et al. 2020, Nava et al. 2022). This is in stark contrast to the trend of rising THC levels in cannabis and represents a pharmacologically and toxicologically novel scenario in the context of modern cannabis use as the research of cannabis related harm has predominantly focused on THC or THC-dominant drug-type cannabis. (Ashton 2001, Pertwee 2006). Interestingly, high CBD to THC ratio cannabis has been discussed in the context of safer use of cannabis (Englund et al. 2017) as well as incorporated into recommendations of lower-risk cannabis use guidelines (Fischer et al. 2017) Nevertheless, there is need for more information about CBD-THC mixture toxicity and central nervous system (CNS) effects in humans at ratios and dosages relevant to light cannabis use.

The scope of this thesis is to review the background of light cannabis, its relationship with drug-type cannabis, synthetic cannabis and other novel cannabinoid products as well as define light cannabis as a distinct concept. Further aim is to characterize the composition of light cannabis with focus on the key cannabinoids THC and CBD. The general properties, pharmacology, and CNS effects of THC and CBD are reviewed along with their pharmacological interactions. Then this thesis investigates the subjective, cognitive, and psychological effects in humans of cannabinoid mixtures like those found in light cannabis by conducting a systematic review of literature. Lastly, the findings of this review are considered in the context of recreational use of light cannabis to elucidate the role of CBD in hazard characteristics of light cannabis products.

# 2 Literature review

Here the chemical composition and diversity in the cannabis plant as well as the key cannabinoids related to this thesis, CBD and THC (Figure 1), are introduced. Their cognitive effects and interactions are also briefly reviewed. Thereafter, the emergence of light cannabis and its relation to other cannabinoid-containing products is discussed. Light cannabis is then defined as a distinct entity from these products and the literature reporting cannabinoid composition of light cannabis samples is summarized. Lastly, effects of light cannabis in humans reported in literature are briefly reviewed.

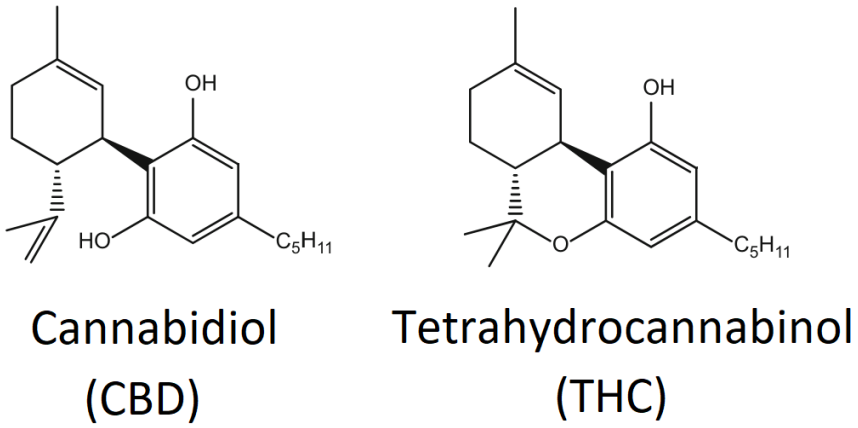


Figure 1. Cannabidiol (CBD) and Δ9-tetrahydrocannabinol (THC).

## 2.1 Chemical composition of cannabis

Cannabis sativa is an herbaceous plant that produces a large number of natural secondary metabolites, representing many different classes of compounds including cannabinoids, terpenes and non-cannabinoid phenols, many of which are known to be pharmacologically active in humans. Concentrations of these compounds vary greatly depending on the plant genetics, growth stage and environmental factors thereby leading to a substantial variability in the chemical composition of plants of different strains and even among individual plants that may be genetically identical but have different growing conditions or represent a different stage of growth (ElSholy et al. 2017). As a result, cannabis or extracts derived from these plants tend to

contain complex and largely unpredictable mixtures of pharmacologically active compounds that may interact by inhibiting, potentiating or acting synergistically to produce effect profiles unique to each combination. The complicated pharmacology of cannabis is dominated by cannabinoids, so they are the most obvious starting point when attempting to unravel this subject.

### 2.1.1 Cannabinoids and cannabis chemotypes

Cannabinoids is the class of compounds present in Cannabis sativa that has received the most attention over the years as it includes the chemical species that are predominantly responsible for the pharmacological effects of cannabis (Pertwee 2006). As the use of various terminology such as “psychoactive” and “psychotropic” in the literature is at best inconsistent and confusing, in this thesis, the distinction is made between psychoactive and intoxicating cannabinoids. Many cannabinoids are psychoactive, meaning that they cross the blood-brain barrier and have pharmacological targets in the central nervous system, but only some of them can induce changes in consciousness, mood or thinking processes or in other words, have intoxicating, mind-altering effects. The term cannabinoid was initially derived from cannabis and referred to a group of structurally related molecules in the plant. Later, development of novel and artificial cannabinoids dubbed synthetic cannabinoids and discovery of endogenously produced cannabinoids in animals and humans called endocannabinoids, revealed many structurally unrelated and vastly different groups of compounds that were pharmacologically like the plant-derived cannabinoids present in cannabis that became known as phytocannabinoids. The nomenclature of cannabinoids was thereby expanded and currently the compound class encompasses all ligands that are capable of binding to and modulating the activity of cannabinoid receptors (Ford et al. 2017).

Structurally, the phytocannabinoids present in cannabis are terpenophenolic compounds and their transformation products as well as derivatives. It is a large group of 125 currently known compounds as recently reported by Radwan et al. (2021) and it includes THC and CBD, which are generally the most abundant cannabinoids in cannabis plants and thus best studied so far and have also been extensively commercialized both legally and illegally. Over the recent years, some other plant-derived cannabinoids such as cannabigerol (CBG), cannabichromene (CBC) and

cannabinol (CBN) have been attracting more scientific and commercial interest as well, after a shift in regulatory framework in the United States loosened the regulation over cannabinoids derived from industrial hemp. CBG and CBC are cannabinoids with no intoxicating properties that share the same biosynthesis pathway with THC and CBD, but are typically present in much lower concentrations and their pharmacological significance is much less well understood as reviewed by Nachnani et al. (2021) and Pollastro et al. (2018a). CBN is suggested to be a psychoactive and intoxicating compound resembling THC although much less potent (Turner et al. 1980). CBN does not have a known biosynthesis pathway in cannabis but is a degradation product of THC (Maioli et al. 2022).

Biosynthesis of cannabinoids in the cannabis plant is well understood for THC and the closely related cannabinoids (Figure 2). All the cannabinoids above are synthesized as aromatic carboxylic acids so they are present in the plant as tetrahydrocannabinolic acid (THC-A), cannabidiolic acid (CBD-A), cannabigerolic acid (CBG-A) and cannabichromenic acid (CBC-A). Geranyldiphosphate and olivetolic acid are precursors for the synthesis of CBG-A by action of a prenylase called cannabigerolic acid synthase. CBG-A in turn, is precursor for the syntheses of THC-A, CBD-A and CBC-A through oxidases dubbed Δ9-tetrahydrocannabinolic acid synthase, cannabidiolic acid synthase and cannabichromenic acid synthase (ElSholy et al. 2017). The acidic forms of the cannabinoids are unstable and form neutral homologues through decarboxylation. Removal of a carboxylic group from a phenyl moiety is a passive process which is accelerated by light or heat, so smoking or cooking the cannabinoids with sufficient heat will readily convert them (Wang et al. 2016). Conversion from acidic to neutral forms is understood to be necessary for pharmacological activity of THC and CBD in humans. For convenience, from now on the cannabinoids are referred to by abbreviations for their neutral forms in this thesis.

Ratio of these synthesis pathway-sharing cannabinoids produced by a cannabis plant is dependent on the relative activity of the above-mentioned synthases in converting the CBG precursor to either THC, CBD or CBC, leading to a differential accumulation of these metabolites, and this in turn appears to be mostly controlled by genetics. The THC:CBD ratios in plant populations follow patterns consistent with the phenotypic cannabinoid ratio being determined

by a single mendelian locus, with co-dominant alleles for both THC and CBD. Phenotypes of plants with homozygotic BT/BT THC predominant genotype or BD/BD CBD predominant genotype at hypothesized B locus are characterized by very large or very small THC:CBD ratios due to a very high proportion of the total cannabinoids being either THC or CBD, whereas heterozygotic BT/BD genotype plants produce relatively even concentrations of THC and CBD (Mandolino et al. 2003, de Meijer et al. 2003). Furthermore, there exists a B0/B0 genotype, with only residual ability to produce CBD and THC due to minimal functionality of the B0 allele so the CBG-precursor accumulates in these plants thus dominating their cannabinoid profile (de Meijer and Hammond 2005). Another known genotype causes the biosynthesis pathway to be severed before the formation of CBG leading to a cannabinoid devoid phenotype (de Meijer et al. 2003). However, while the above-described single locus model has been accurate and successful for many practical applications, and certainly suffices to explain the inheritance of cannabis chemical genotype in the context of this thesis, recent studies suggest that more complicated processes contribute to the chemical genotype inheritance of cannabis as well (Campbell et al. 2020)

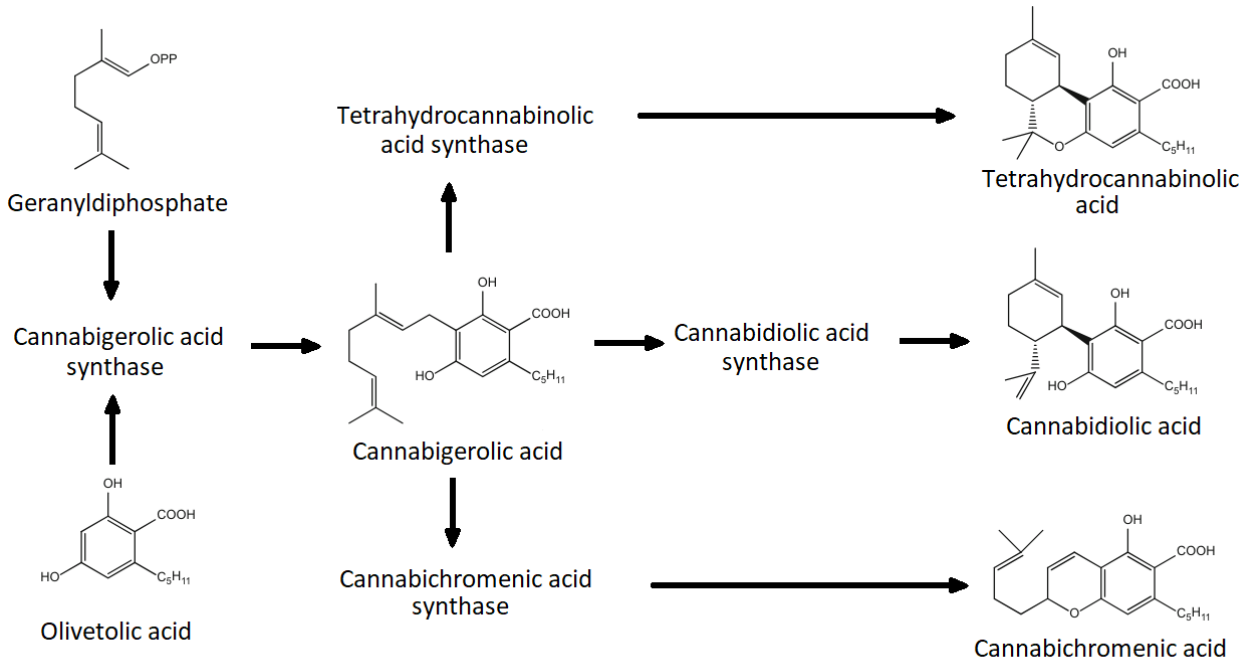


Figure 2. Biosynthesis pathway of cannabigerol, tetrahydrocannabinol, cannabidiol, and cannabichromene (modified from ElSholy et al. 2017).

Five distinct chemical phenotypes arising from these genotypes, dubbed chemotypes, have been established to differentiate the cannabis plant varieties by their cannabinoid composition. Three chemotypes based on THC:CBD ratios were originally introduced by Small and Beckstead (1973). According to their classification, chemotype I is characterized by a high THC:CBD ratio and a high THC concentration exceeding 0.3% of dry weight and chemotype II is an intermediate type with THC:CBD ratio ranging from 0.5 to 2 whereas chemotype III has a high CBD:THC ratio and a low THC concentration of below 0.3%. However, these three chemotypes are often adjusted and applied based on the THC:CBD ratios only, not adhering to the strict cutoff levels for cannabinoids (Mandolino et al. 2003, de Mejer et al. 2003, Pacifico et al. 2007). Chemotype IV has CBG as the predominant cannabinoid and was first identified by Fournier et al. (1987) and cannabis plants with negligible cannabinoid production resulting in total cannabinoid content below 0.2% are classified as chemotype V (Mandolino and Carboni 2004). The ratio of THC and CBD is predictable for populations with stabilized homozygotic genotypes and therefore the chemotypes of cannabis with very high or very low THC:CBD ratios are stable in closed populations across generations. (Mandolino et al. 2003, de Meijer et al. 2003). The concentration of a particular cannabinoid in each plant is dependent on the ratio of the various cannabinoids present and the total fraction of cannabinoids in the plant biomass. The total cannabinoid content is a polygenic trait and follows a normal distribution in populations (de Mejer 2003). It is also heavily affected by growth stage and environmental conditions (ElSholy et al. 2017).

### 2.1.2 Tetrahydrocannabinol

Tetrahydrocannabinol or Δ9-tetrahydrocannabinol is a tricyclic terpenophenolic compound (Figure 1). This structure renders the molecule very hydrophobic and thus lipophilic. Garrett and Hunt (1974) demonstrated that THC is practically insoluble in water, with an estimated solubility of 1.05mg/l in physiological saline solution and has a PKa of 10.6. THC is reported to have a n-octanol/water partition coefficient as high as 9.44*10^6 (LogP = 6.97) (Thomas, Compton and Martin 1990). According to the PubChem database the molar mass of THC is 314.5 g/mol. Tetrahydrocannabinol is the psychoactive and intoxicating cannabinoid that is primarily responsible for the mind-altering effects of cannabis (Wachtel et al. 2002) and THC concentration in the dried inflorescence is used as a measure of psychoactivity of cannabis (ElSholy et al. 2017).

Use of cannabis results in tolerance and may cause withdrawal symptoms that are associated with THC (Ashton 2001).

The most important pharmacological targets of THC are cannabinoid receptors of the endocannabinoid system. Endocannabinoid system is widespread in the CNS, has a neuromodulatory function and plays roles in development of the CNS, synaptic plasticity and a variety of endogenous regulatory processes. Arachidonoyl ethanolamide (AEA) and 2-arachidonoyl glycerol (2-AG) are the best studied endogenous cannabinoids that act as messenger molecules of the endocannabinoid system and partial agonists of the cannabinoid receptors 1 and 2 (CB1 and CB2). THC has a similar partial agonist effect on these receptors and is therefore functionally analogous to AEA and 2-AG. CB1 and CB2 are both G-protein coupled receptors and CB1 receptors are the predominant type of the two in the CNS with only a small number of CB2 receptors being found there. Most of the CB2 receptors are expressed in peripheral tissues and immune cells (Lu and Mackie 2016). The characteristic intoxicating effects of THC are due to its pharmacological action as a partial agonist of CB1 (Pertwee 2008). Ingestion of a sufficient dose of THC induces a subjective change in the mental state and perception of the user and alters cognition as well as psychomotor performance. While the cognitive effects like short-term memory deficits and the perceptual changes like impaired perception of time are somewhat consistent effects, the subjective experience may be euphoric and anxiety decreasing on some occasions, but dysphoric and panic or paranoia inducing on others. The duality of these effects and the severity of adverse reactions are partially dose-related, but also dependent on the user and their mental state (Ashton 2001).

The CNS effects of THC are evident even at very low doses. Kleinloog et al. (2014) reported that based on their analysis of combined data from 10 experimental human studies on infrequent users, 58% of volunteers responsive to a THC treatment showed subjective effects that significantly differed from placebo at a 2 mg dose of purified THC administrated via inhalation and dose-response was evident in 2 – 6 mg dose range. 6 mg dose was well tolerated with less than 20% of the volunteers responsive to THC reporting dysphoric effects and 30% reporting feeling anxious at this dose level. Similarly, Freeman and Lorenzetti (2020) suggested, based on

multiple experimental human studies, that inhaled and oral doses of 2 – 8 mg of THC are sufficient to produce intoxicating effects in infrequent cannabis users, but unlikely to lead to severe adverse responses. The potency of THC is dependent on the route of administration and, based on pharmacokinetic modeling, orally ingested dose has been estimated as 5.71 times as intoxicating as the same dose administered via inhalation. This was assumed to be largely due to first-pass metabolism and the enhanced formation of 11-OH-THC metabolite, which has been estimated to be four times as potent as THC. However, instead of subjective measures of intoxication, the estimated intensity of effects based on cannabinoid plasma levels was used as a basis of this assessment (Orens et al. 2015).

Toxicity of THC is conventionally understood to be extremely low and systemic pharmacodynamic effects are mainly limited to the cardiovascular system and typically result in tachycardia and occasional postural hypotension (Ashton 2001). However, intentional and unintentional ingestion of even a single dose of THC or cannabis may cause adverse reactions promoting severe distress or even requiring critical care and, as cannabis is becoming more widely legalized and high-potency THC products more readily available, acute poisonings have subsequently become more commonplace. An observational study on Oregon/Alaska Poison Center data from 2015-2017 showed that different presentations of toxicity were observed in different age groups with adults and adolescents presenting with tachycardia and CNS excitation or depression. Children, on the other hand, mostly presented with CNS depression and, worryingly, respiratory depression was associated with some cases requiring intensive care and intubation (Noble, Hedberg and Hendrickson 2019). Since the early 2000s, cannabis toxicity has also been associated with myocardial infarction in young people with little predisposition to cardiac events, leading to death in some cases. (Chetty, Lavoie and Dehghani 2021). Despite these emerging concerns, THC and cannabis are best associated with and have been most extensively studied for their effects on the cognitive- and mental health. Repeated dosing of cannabis and particularly the THC it contains has been associated with numerous adverse outcomes and higher THC concentration in cannabis as well as higher frequency of use are associated with increased incidence and severity of these outcomes (Curran et al. 2016). The cognitive and psychological effects of cannabis are introduced in more detail later in section 2.2.

### 2.1.3 Cannabidiol

Cannabidiol is structurally very similar to THC. However, CBD is a bicyclic terpenophenolic compound as opposed to tricyclic THC because the dimethylpyran ring structure of THC is not cyclized in a CBD molecule (Figure 1). Despite the slight differences in structure, the molar mass of CBD is the same as that of THC at 314.5 g/mol according to PubChem database. CBD is very lipophilic with a LogP of 6.3 and its most acidic hydrogen donor has a PKa of 9.1 (Odi et al. 2020). Cannabidiol is a psychoactive cannabinoid that has been suggested to have anxiolytic (Zuardi et al. 1993, Zuardi et al. 2017, Linares et al. 2019)) and antipsychotic effects in humans (Leweke et al. 2012, McGuire et al. 2018). CBD has been generally regarded as non-intoxicating and exhibiting no abuse or dependence potential (WHO 2018).

Like THC, CBD also has important targets in the endocannabinoid system. However, unlike THC, CBD does not bind to the orthosteric ligand binding site of CB1 or CB2 very effectively, having only low affinity. Instead, it acts as a negative allosteric modulator of CB1 in the presence of receptor agonists like AEA or THC and can inhibit the binding or receptor activation by these orthosteric ligands. Moreover, CBD acts as an inhibitor of enzymes fatty acid amide hydrolase (FAAH) and monoacyl glycerol lipase (MAGL) that break down AEA and 2-AG, respectively. CBD also binds to fatty acid binding proteins that act as the carriers of AEA to FAAH, further inhibiting AEA reuptake and turnover. CBD can therefore increase the signaling of endocannabinoid agonists of CB1 by increasing their concentration and availability (Gingrich et al. 2023). CBD does not have a direct THC-like effect on CB1, and many psychopharmacological effects of CBD seem best explained by other mechanisms instead of the interactions with cannabinoid receptors. CBD is an agonist of serotonin receptor 1A (5-HT1A) and activates transient receptor potential vanilloid (TRPV) channels, particularly TRPV1 for which it is a low-potency full agonist. Preclinical in vivo studies suggest that the anxiolytic effects of CBD are primarily due to 5-HT1A agonism and the antipsychotic effects are partially related to a TRPV1 mediated mechanism (Britch et al. 2021).

Because oral CBD does not produce discernible subjective effects or intoxication, it is difficult to determine a dose threshold for its psychoactive effects. Human clinical studies exploring the

anxiolytic and antipsychotic potential of CBD have utilized a wide range of doses and yielded both positive and negative results (Britch et al. 2021). Studies that have identified anxiolytic effects and used oral doses at multiple dose levels ranging from 100 mg to 900 mg of CBD, have reported inverted U-shaped dose-response curves where doses of 300 mg have shown anxiolytic effects whereas the higher and lower doses have not (Zuardi et al. 2017, Linares et al. 2019). Antipsychotic effects have been reported at 800 mg daily oral dose that provided similar improvement to clinical symptoms of schizophrenia as amisulpride (Leweke et al. 2012) and 1000 mg oral dose daily for six weeks improved positive psychotic symptoms in another study (McGuire et al. 2018). Neither of these studies used more than one dose level so a possible dose-response could not be determined. While oral CBD appears to be consistently non-intoxicating in humans, two recent studies have suggested subjective effects resulting from inhalation of vaporized CBD. Inhalation of 100 mg produced subjective drug like- and pleasant drug effects (Spindle et al. 2020) and inhalation of 400 mg was reported to produce intoxication characterized by dissociative symptoms (Solowij et al. 2019), but the single-dose nature of the CBD-only interventions prevent determining a possible dose-response for these effects in either study.

Toxicity of CBD is low and, in one phase 1 clinical study, single oral doses of up to 6000 mg CBD, corresponding to a dosage of about 85 mg/kg for a 70-kg person, were reported to only result in mild or moderate adverse events including gastrointestinal disorders like diarrhea and nausea as well as nervous system disorders such as somnolence, headache and dizziness in healthy adults (Taylor et al 2018). Adverse effects reported in the clinical trials of CBD have recently been reviewed by Huestis et al. (2019) and for repeated dosing of up to 50mg/kg/day for periods ranging from weeks to more than one year, the behavioral and gastrointestinal symptoms were somewhat similar as with single doses. Repeated dosing was also associated with hepatic effects, with some instances of increased blood transaminases and other liver enzymes indicative of inflammation or damage to cells in the liver and possibly drug-induced liver injury. Notably, in the reviewed studies, CBD was used concomitantly with other medication including valproate so the possible hepatic toxicity and some other adverse effects may have been due to these other medications or their drug-drug interactions with CBD (Huestis et al. 2019). However, another clinical trial in healthy adults suggested that daily repeated oral dosing of 1500 mg of CBD,

corresponding to about 20 mg/kg for a 70 kg person, can be associated with liver abnormalities even in the absence of other medications (Watkins et al. 2021).

## 2.2 Neurophysiological basis of acute- and long-term CNS effects of cannabis

Because the endocannabinoid system is involved in cognitive processes such as memory, learning as well as attention, and has an important role in the development and maturation of the nervous system, cannabis-related disturbances of the endocannabinoid function may result in acute-, long-term-, and age-dependent effects including cognitive harm or psychiatric disorders (Curran et al. 2016). Endocannabinoid signaling regulates both neurotransmitter signaling and synaptic plasticity with generally inhibitory effects. As endocannabinoids are prevalent throughout the brain, they have a large impact on the synaptic function in the CNS (Castillo et al. 2012). CB1 mediated THC induced dysregulation of the neurotransmitter signaling is implicated in the effects of both acute- and chronic exposure to cannabis, but the brain areas and neurotransmitters affected differ to some extent between the two (Curran et al. 2016).

Precise spatiotemporal control of synaptic plasticity and thus well-regulated endocannabinoid signaling is critical for the wiring and function of neural networks as well as the development of the nervous system (Harkany, Mackie and Doherty 2008). As these processes are also involved in the maturation of cortical circuits, it has been suggested that THC and similar compounds can induce developmental abnormalities possibly contributing to lasting cognitive impact or psychiatric disease (Lu and Mackie 2016) and these age-dependent effects are more pronounced in adolescents than in adults (Curran et al. 2016). The cognitive effects of cannabis use generally arise from functional perturbations but may even have structural alterations of the CNS associated with them (Curran et al. 2016). Numerous neuroimaging studies included in the systematic review by Batalla et al. (2013) reported functional and structural aberrations in brains of both adolescent and adult cannabis users but suffered from methodological limitations and heterogeneity of findings.

Acute effects of cannabis are predominantly induced by THC and its intoxicating as well as clinically relevant toxic CNS effects are already introduced in section 2.1.2. The acute effects of cannabis are transient and last from minutes to hours depending on the dose and the route of administration. The effects are based on THC induced changes in neurotransmitter signaling and disruption of plasticity, particularly in the brain regions expressing high densities of CB1, like hippocampus and prefrontal cortex. Interference with the normal function of- and the communication between these brain areas produces a range of effects such as disturbances of working- and episodic memory as well as impaired learning and attention (Curran et al. 2016, Kroon, Kuhns and Cousijn 2021). Cognitive dysfunction and psychological symptoms are dose-related, possibly escalating into psychotic states (Hudak, Severn and Nordstrom 2015, Favrat et al. 2005) or coma (Tweet, Nemanich and Wahl 2023) at very large doses, especially in susceptible individuals. Pronounced psychotic reactions have been associated with orally ingested cannabis and the resulting increased 11-OH-THC metabolite effects compared to inhalation, but these reactions generally resolve spontaneously or with symptomatic treatment, without lasting effects (Hudak, Severn and Nordstrom 2015, Favrat et al. 2005).

Repeated use of cannabis can cause long-term effects that likely arise from multiple processes that appear to be proportional to the recent level of use or the accumulated dose. Changes in neurotransmitter signaling, CB1 downregulation, and structural changes in the brain resulting from sustained use are implicated in the persisting effects of cannabis use (Curran et al. 2016). Observations in primates also suggest that long-term effects may partially arise from prolonged THC effects due to its slow clearance from the brain tissue (Withey et al. 2020). Many memory-, learning- and executive function deficits have been associated with chronic cannabis use, but the poor quality of evidence and inconsistent findings hamper establishing causation for many effects (Curran et al. 2016, Kroon, Kuhns and Cousijn 2021). While it seems that these long-term effects are mostly reversible in adults, likely owing to the transient nature of the likely causative factors like THC presence in the brain or CB1 downregulation, adolescent use of cannabis is associated with increased cognitive impact compared to adults. Possibly irreversible deficiencies can result from THC interference with neurodevelopmental maturation of cognitive processing during sensitive periods of synaptic pruning and white-matter development. Adolescent onset of

use has been reported to cause increased negative impact on visuospatial attention, verbal fluency and inhibition compared to adult onset of use (Curran et al. 2016). Furthermore, a large, longitudinal neuroimaging study found adolescent use of cannabis to be dose-dependently associated with increased cortical thinning in the prefrontal cortex areas rich in CB1 receptors and attentional impulsiveness, but not with other psychopathologic or neurocognitive measures (Albaugh et al. 2021).

Cannabis is understood to have a comparatively low addiction potential. Estimated probability of lifetime exposure to cause addiction is 8.9% for cannabis users while the same is true for 22.7% and 67.5% of users of alcohol and tobacco, respectively. This is likely related to the relatively low CB1 expression in the reward and addiction associated mesolimbic regions ventral tegmental area and nucleus accumbens as well as the rather modest coupling of the endocannabinoid system to dopamine signaling compared to the mechanisms of many other drugs of abuse. However, several other factors may promote problematic or excessive patterns of cannabis use. Prolonged- or substantial exposure to cannabis may cause decreased dopamine signaling and increased release of corticotropin-releasing factor during THC abstinence, producing negative affective states and prompting sustained use of cannabis. Dysregulation of the endocannabinoid system by excess CB1 agonists leads to buildup of tolerance and may cause withdrawal symptoms including appetite, mood, and sleep disturbances. Furthermore, chronic THC exposure has been observed to be associated with impaired decision-making as well as reduced inhibitory control which are cognitive deficits that may contribute to the development of cannabis use disorder (CUD). Higher THC concentration in cannabis produces stronger reinforcement, contributing to the development of addiction and is also associated with greater addiction severity (Curran et al. 2016). For more in-depth review of cognitive- and psychological effects of cannabis use, see Curran et al. (2016).

## 2.3 Interactions of THC and CBD

The possible interactions of clinical significance between THC and CBD are likely mostly pharmacodynamic in nature as there is very little evidence suggesting the contribution of

pharmacokinetic mechanisms in humans (Boggs et al. 2018). As the best investigated interactions between CBD and THC are currently those related to the function of the endocannabinoid system, they are reviewed here. However, as the exact mechanisms remain unelucidated, it is not currently understood to which extent the possible CBD modulation of THC effects is based on targets in the endocannabinoid system and may well be mediated to an unknown degree by interactions with other targets such as the serotonergic or endovanilloid systems like the suggested anxiolytic and antipsychotic effects of CBD (Britch et al. 2021). Numerous human studies have investigated the modulation of THC effects by CBD and reported a variety of outcomes ranging from mitigation to potentiation, but also many negative results.

The overwhelming majority of interventional studies do not support clinically significant pharmacokinetic interaction between THC and CBD in humans (Agurell et al. 1981, Hunt et al. 1981, Nadulski et al. 2005, Karschner et al. 2011). Nadulski et al. (2005), for example, pointed out that the CBD effect on THC pharmacokinetics was small compared to other factors causing variability in their results. In contrast, mechanistic studies indicate pharmacodynamic interactions between THC and CBD. Numerous preclinical studies have investigated the CBD interaction with CB1 receptors. While CBD binds only weakly to CB1, it has been shown to be able to modulate THC effects in the CB1 receptor (McPartland et al. 2015) by a negative allosteric mechanism (Laprairie et al. 2015, Tham et al. 2019). CBD induced increase of the endocannabinoid tone (Gingrich et al. 2023) can lead to further modulation of the THC-CB1-interaction through increased competition for binding sites by orthosteric CB1 ligands such as AEA and 2-AG (Pertwee 2008). Moreover, CBD has multiple targets in the CNS, that are not part of the endocannabinoid system but may still contribute to the modulation of THC intoxication to some extent that is currently not understood (Britch et al. 2021, Boggs et al. 2018). Additionally, neuroimaging results have suggested that CBD and THC elicit diametrically opposing functional changes in various brain regions which could imply interaction at the level of neural substrate of cognitive processing (Bhattacharyya et al. 2010).

Studies investigating the effects of CBD-THC mixture intoxication in humans using a range of different methods have reported mixed outcomes. Morgan and Curran (2008) and Morgan et al.

(2010, 2012) carried out highly innovative observational and naturalistic studies to investigate the effects of different types of street cannabis. They characterized different cannabis types based on the measurements of CBD concentrations of users' own cannabis (Morgan et al. 2010) and determined user cannabinoid exposures by the THC and CBD concentrations in their hair (Morgan and Curran 2008, Morgan et al. 2012) and concluded that higher CBD concentration in user cannabis as well as CBD presence in hair samples was associated with fewer psychotic symptoms and cognitive deficits (Table 1). Later, several clinical studies have produced mixed results where CBD has been reported to attenuate the effects of THC (Englund et al. 2013, Hindocha et al. 2015), but also not to improve the psychological or cognitive impairments caused by THC (Haney et al. 2016, Morgan et al. 2018, Englund et al. 2023). One study reported potentiation of the THC effects at low doses of CBD, but attenuation at large doses of CBD (Solowij et al. 2019). Notably, negative findings have been reported by two recent studies where graduated CBD doses were administered with THC to the participants, but no modulatory effects were observed (Haney et al. 2016, Englund et al. 2023). For additional information on the topic, the pharmacokinetic and -dynamic interactions of THC and CBD are examined in detail in a review by Boggs et al. (2018).

Table 1. Some studies investigating the interactions between CBD and THC in humans.

| Study | Type of study | Population | Intervention or CBD exposure | CBD modulation of THC effect | Reported CBD effects |
|---|---|---|---|---|---|
| Morgan and Curran 2008 | Observational cross-sectional study | Current and former ketamine users, users of other drugs and non-users (n=140) | Hair sample analysis was used to determine THC only, THC+CBD or no cannabinoid exposure. | Yes/no (Attenuation) | Significantly lower psychotomimetic symptoms associated with THC+CBD compared to THC alone. |
| Morgan et al. 2010 | Observational cross-sectional naturalistic exposure study | Cannabis users (n=137) Comparison between subgroups high CBD (n=22) vs. low CBD (n=22) | Users smoked their own cannabis. Cannabinoid exposure was determined by samples of cannabis and saliva | Yes/no (Attenuation) | Improved cognition and memory associated with high vs. low CBD. No CBD effect on psychotomimetic symptoms of THC. |

| Study | Type of study | Population | Intervention or CBD exposure | CBD modulation of THC effect | Reported CBD effects |
|---|---|---|---|---|---|
| Morgan et al. 2012 | Observational cross-sectional study | Recreational (n=54) and daily users (n=66) of cannabis | Hair sample analysis was used to determine CBD presence and high or low levels of THC | Yes/no (Attenuation) | CBD was associated with attenuation of psychotic symptoms and improvement of recognition memory. |
| Englund et al. 2013 | Clinical study | Adult participants with minimum of one previous cannabis use (n=48) | Oral CBD (600 mg) + intravenous THC (1.5 mg) | Yes/no (Attenuation) | CBD decreased THC-induced episodic memory impairment, paranoia and psychotomimetic effects. No CBD effect on immediate recall impairment. |
| Hindocha et al. 2015 | Clinical study | Volunteers characterized by heavy or light cannabis use frequency and high or low schizotypy (n=48) | Inhaled (vaporized) THC (8 mg), CBD (16 mg) or THC+CBD (8 + 16 mg) | Yes/no (Attenuation) | CBD prevented facial affect recognition impairment by THC but did not decrease subjective intoxication. |
| Haney et al. 2016 | Clinical study | Non-treatment seeking, healthy cannabis smokers (n=31) | Oral CBD (200, 400, 600 or 800 mg) + smoked (THC) cannabis (0.01% or 5.30-5.80%) | No | CBD did not reduce the reinforcing, physiological, or positive subjective effects of smoked cannabis. |
| Morgan et al. 2018 | Clinical study | Volunteers characterized by heavy or light cannabis use frequency and high or low schizotypy (n=48) | Inhaled (vaporized) THC (8 mg), CBD (16 mg) or THC+CBD (8 + 16 mg) | No | CBD did not improve psychotomimetic symptoms or memory impairment effects of THC. |

## 2.4 Cannabinoid mixtures and interactions

Although the scope of this thesis is focused on THC and CBD, it is worth noting that while they are the most abundant active compounds in cannabis, pharmacology of THC and CBD alone is a gross simplification of the pharmacology of cannabis in its full complexity. There is a plethora of phytocannabinoids, terpenes and various compounds present in cannabis and its extracts that can exert pharmacological effects and interact with one another (McPartland and Russo 2001). Especially in the context of therapeutic use of cannabis, the mixture effect is known as the entourage effect and involves not only the interactions between phytocannabinoids, but also phytocannabinoid-terpenoid interactions that give rise to effects that are often unique or exceed those expected based on the individual cannabinoids present in the mixture (Russo 2011).

Of particular interest in terms of cannabis effects on cognition are the cannabinoids that interact with CB1 and may thus have direct pharmacodynamic interactions with THC or can be used as substitutes of THC. Examples of such compounds are CBN and Δ8-tetrahydrocannabinol (Δ8-THC) that are partial agonists of CB1 (Husni et al. 2014) and both are minor constituents in natural cannabis (Mechoulam 1970). Hexahydrocannabinol (HHC) is also a CB1 partial agonist and a constituent in natural cannabis occurring at low concentrations (Basas-Jaumandreu and de Las Heras 2020). In contrast, tetrahydrocannabivarin (THCV) is a naturally occurring minor cannabinoid with CB1 antagonist effects (Pertwee 2008) and shown to inhibit or potentiate various THC effects in humans (Englund et al. 2016). Concentrations of other cannabinoids in natural cannabis are not predictable from the THC:CBD ratio and can vary greatly between each plant even within plants grown from seeds derived from the same parent plants and exhibiting similar THC:CBD ratios and thus genetically very similar in this regard (Mandolino et al. 2003). Therefore, analysis of all the constituents is always necessary for reliable characterization of pharmacological properties for each different cannabis derived mixture.

Details about pharmacological interactions of cannabinoids other than THC and CBD are beyond the scope of this thesis as is the role of terpenes and other compounds. However, it is imperative to consider the role of other mixture components in relevant scenarios such as when cannabis plant extracts are used in interventional studies instead of purified cannabinoids.

## 2.5 Light cannabis

Light cannabis is a novel type of cannabis product that became available a little over a decade ago so, to open the discussion on this topic, the background for its emergence and relationship to other related products should be considered. Above it has been established, that cannabis varies greatly in composition and that THC and CBD concentrations are no exception, but because of the genetic basis of their synthesis pathways, concentration ratios of these cannabinoids have predictability in cannabis plant varieties and populations. In the past decades, plants of chemotype I have been favored in the development of new cultivars of drug-type cannabis with very high THC concentrations and THC:CBD ratios as the mind-altering effects of THC have been the most demanded quality in cannabis products. In contrast, CBD began to garner interest only much later, after some initial studies had suggested it to be associated with various potential health benefits. Nevertheless, despite the complicated regulatory status of CBD (Corroon and Kight 2018) and even direct interventions by regulatory agencies (US FDA 2023) the CBD industry in the USA grew rapidly during the past decade and became a multi-billion-dollar industry by 2020s (Corroon and Kight 2018). The emergence and increasing availability of light cannabis and associated cannabinoid products including semi-synthetic cannabinoid (SSC) products are closely linked to the rise of the CBD industry and several important legislative changes that took place in Europe and the United States during the 2010s.

In Europe, the low-THC cannabis products had been dubbed as “light cannabis”, “cannabis light” or “C-light” soon after Switzerland made a legislative chance in 2011, raising the allowed level of THC in industrial hemp from up to 0.3% to up to 1.0% and low-THC cannabis products became available (Monti et al. 2022). Italy introduced changes in the legislation regulating domestic industrial hemp in December 2016. The law, intended to regulate and incentivize hemp production and commercialization, increased the allowed maximum THC concentration of industrial hemp on the domestic market to 0.6% but omitted regulating the production of hemp flowers. This created a legislative gap that allowed the sale of flowers of industrial hemp plants and products derived from them for other purposes but not explicitly for consumption. Thus, the sale of industrial hemp products that were marketed as having high CBD content began in the early summer of 2017 (Carrieri, Madio and Principe 2019, 2020).

In response to this development, the European Union legislation related to granting payments to farmers for growing products not exceeding 0.2% of THC was then widely assumed to imply that these types of products could be legally advertised and sold in the other member states as well. However, like the Swiss and the Italian legislation, the EU legislation was not intended to be conducive of this. Nevertheless, this gray area of regulation prompted the spread of the low-THC cannabis products to Austria in 2017 and Germany, France and Belgium in 2018. By February 2019 at least one type of low-THC cannabis product was known to be advertised for sale in every EU country except for Estonia, Finland and Latvia (Hughes et al. 2020).

Another key event laying the foundation for the current expansion of this industry was the approval of the United States Agriculture Improvement Act of 2018 also known as the “2018 Farm Bill”, which removed hemp from the federal list of controlled substances. This allowed commercial sale and use of hemp-derived products and made hemp-derived cannabinoids also legal by extension as the Farm Bill defined as hemp all parts of Cannabis sativa including derivatives, extracts and cannabinoids that do not exceed a limit of 0.3% THC by dry weight. Therefore, because of this bill, hemp-derived CBD became effectively legal as it was removed from regulation under the controlled substances act (Dickson, Janasie and Willett 2019).

CBD became cheap and abundant, not only for use as an ingredient in products, but also as a precursor to SSCs as Farm Bill also introduced a legal loophole that is assumed by legal experts to allow the SSC derivatives of CBD as well (LoParco et al. 2023). These SSCs could then be used to adulterate Low-THC cannabis products (Ujváry et al. 2023) or in a variety of other products (Johnson-Arbor and Smolinske 2022, LoParco et al. 2023) and sold in the same commercial outlets as Low-THC cannabis products. Currently, low-THC cannabis and products containing SSCs are widely available both in the United States and the European Union and a wide variety of product types are available including industrial hemp flowers, resin, extracts, edibles as well as vape liquids (Hughes et al. 2020, Johnson-Arbor and Smolinske 2022, Ujváry et al. 2023). For more details, CBD status in the United States is reviewed by Dickson, Janasie and Willett (2019) and the developments regarding low-THC cannabis products in Europe by Hughes et al. (2020)

### 2.5.1 Composition-based taxonomy of novel cannabinoid products and definition of light cannabis

Currently, light cannabis does not have an established definition in the scientific literature so the use of this term and the related concepts should be considered to outline their characteristics based on composition as well as legislative- and pharmacological aspects. In the simplest terms, “Light cannabis” refers to low-THC cannabis products and is a term introduced in the media and used in scientific literature as well. EMCDDA uses the term “low-THC cannabis products” to refer to “products being or containing cannabis herb, resin, extracts or oils that claim or appear to have a very low percentage of THC, and which would be unlikely to cause intoxication” (Hughes et al. 2020). Definition for scientific use of the term low-THC cannabis is not well established and there is some debate over what it encompasses (Hughes et al. 2020). However, products sold as low-THC cannabis products seem to be, in the broadest terms, cannabinoid containing products purportedly regulated by legislation designed to regulate industrial hemp thus exempting these products from being subject to narcotics laws and regulations that treat cannabis and cannabinoids as controlled substances.

Synthetic cannabinoid products are in principle a similar phenomenon to low-THC cannabis products, intended to evade the legislative and regulatory control measures for illegal narcotics. They contain purely artificial cannabinoids, that intend to mimic the intoxicating effects of THC but are often CB1 full agonists with potential to induce life-threatening toxicity (Ford et al. 2017). In contrast, the low-THC cannabis products contain naturally occurring cannabinoids or their mixtures derived from hemp plants and are thus distinct from synthetic cannabinoid products and the occasional reports of low-THC products adulterated with CB1 full agonist-synthetic cannabinoids (Gerace et al. 2022, Monti et al. 2022, Oomen et al. 2022) are not representative of typical low-THC cannabis products available on open markets (Hughes et al. 2020). Moreover, the emergence of new products containing SSCs with worrying or unknown pharmacological properties warrants using caution in communication and a distinction should be made where these novel products are not included in the definition of light cannabis or low-THC cannabis products as this could easily miscommunicate the potential dangers associated with them.

SSCs can be produced using easily and abundantly available cheap CBD as a precursor, have similar, but typically less potent, intoxicating effects as THC and are used as alternatives to THC (LoParco et al. 2023, Pollastro et al. 2018b, Ujváry 2023). Hence, products containing these SSCs have also been colloquially referred to as “alternative THC-products” (Johnson 2021). While many SSCs are compounds that are also naturally present in the cannabis plants in small concentrations, such as HHC (Basas-Jaumandreu and de Las Heras 2020), Δ8-THC and CBN (Mechoulam 1970), some CBD derived SSCs detected on the market, such as Hexahydrocannabinol acetate, have not been observed to occur naturally (Ujváry et al. 2023). Furthermore, another SSC Hexahydrocannabiphorol is much more potent than THC, blurring the line between SSCs and synthetic cannabinoids (Ujváry et al. 2023).

SSCs can be included in various products, such as infused candies or vape pens containing solely or primarily these manufactured cannabinoids. SSCs can also be added to various Low-THC cannabis products to enhance their mind-altering effects, and these are often sold alongside the regular low-THC cannabis products (LoParco et al. 2023, Ujváry 2023). Light cannabis adulterated with and containing abnormally high concentrations of these SSCs should be considered separately from chemically unmodified light cannabis as their pharmacological properties may markedly differ from natural cannabinoid mixtures directly derived from hemp. It is also obvious that a new umbrella term containing both low-THC cannabis products and SSC products should exist to help avoid inclusion of the latter group in the former, so in this thesis they are referred to as “novel cannabinoid products” signifying the recent emergence of these product groups.

Acknowledging the above considerations, following taxonomy can be outlined for novel cannabinoid products based on their cannabinoid compositions, where two product groups divided to a total of four distinct types of products can be identified (Figure 3). The first type is products containing the entire mixture of naturally occurring, or as it is commonly referred to, full spectrum, of hemp-derived cannabinoids irrespective of whether the mixture is derived from a single plant or is a composite of that of multiple plants. Examples of such products are hemp flowers or resin, and this type includes light cannabis as well when defined as suggested by this thesis. While colloquially light cannabis has been an umbrella term covering a variety of low-THC

cannabis products and SSC products, in the context of expanding product base and increasing necessity of distinguishing terminology, light cannabis should instead be understood as a subset of the low-THC cannabis products. The second type is products with isolated cannabinoids like CBD edibles containing purified and chemically unmodified single cannabinoids separated from the cannabinoid mixtures extracted from industrial hemp. Multiple isolated cannabinoid species may also be combined in some of these products such as CBD+CBG oil infusions. These first two types could be included in the EMCDDA definition of low-THC cannabis products (Hughes et al. 2020) and thus the group they belong in is named accordingly (Figure 3).

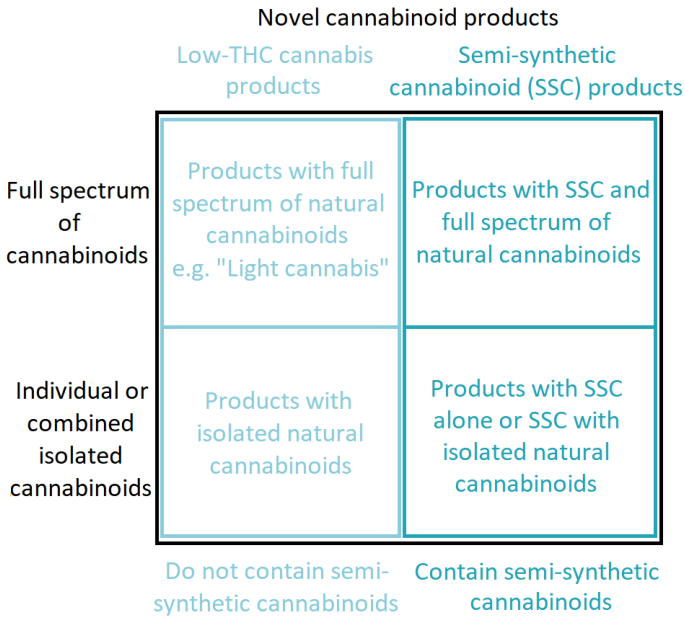


Figure 3. The cannabinoid composition-based taxonomy of novel cannabinoid products.

The third type is products containing the full spectrum of hemp-derived cannabinoids with added SSCs. Hemp flowers with added HHC or CBN are examples of such products. The Fourth type is products containing purified SSCs alone or in combination with purified unmodified single cannabinoids and examples of these products include Δ8-THC candies, HHC vape pen cartridges and edibles containing mixture of both Δ8-THC and CBD. The inclusion of the latter two types of products in the EMCDDA definition would be problematic since they could possibly cause intoxication due to the functional analogs of THC they contain, despite not being intoxicating explicitly due to THC (Hughes et al. 2020). Following this logic, low-THC cannabis- and

SSC products are separated into two product groups in this categorization (Figure 3). It should be noted that this classification is based on the advertised product type characteristics and the actual composition of the products corresponding to various types is often ambiguous for reasons further elaborated in section 2.5.2.

One of the difficulties in defining light cannabis or low-THC products in general is differentiating them from regular drug-type cannabis, which could be done by determining their THC concentration range as is done in the legislative setting. Using the tolerated threshold levels for industrial hemp as a basis for this is, however, problematic as there are regional differences in the highest THC concentration that can legally be present in hemp. The highest allowed THC concentration is in effect in Switzerland where low-THC cannabis of under 1% of THC by dry weight is legal (Swiss Fedlex 2011). In the United States, the 2018 Farm Bill set the limit to 0.3%, below which any cannabis or cannabis derived product is regarded as hemp and not subject to controlled substances act. In the European Union the maximum allowed concentration of THC in industrial hemp was 0.2% by dry weight (Hughes 2018) until it was increased to 0.3% as a part of the Common Agricultural Policy measures that came into effect in 2023 (European Commission 2023). However, there is also some variability in the national legislations between the member states of the European Union as Italy allows industrial hemp products of up to 0.6% of THC by dry weight (Carrieri, Madio and Principe 2019) whereas in Finland the enforced allowed THC level is 0% in hemp products.

Due to the differences in the tolerated levels of THC, products that could be defined as light cannabis in one region may be illegal drug-type cannabis in others. However, since dose matters more than concentration when ingestion by humans is considered, a defined cutoff threshold between light- and drug-type cannabis is pharmacologically somewhat arbitrary. Moreover, as discussed above in section 2.1.1, the key distinction between drug-type cannabis (chemotype I) and hemp-type cannabis (chemotypes III and IV) are the opposing ratios of THC and CBD or CBG concentrations. Therefore, not the THC concentration, but the ratio of THC and other cannabinoids CBD or CBG could provide a sound and more pharmacologically meaningful metric to distinguish light cannabis from drug-type cannabis.

Concluding this summary, as a definition for light cannabis is necessary for further characterization of its composition, one based on the above considerations is suggested here. In this thesis, the term light cannabis refers to raw industrial hemp and products derived of it such as resin, containing the full spectrum of cannabinoids present in the hemp plant. In light cannabis, CBD:THC or CBG:THC ratios must be at least 2, which is the same as the limit for defining the plant as CBD-dominant type as opposed to THC-dominant type or intermediate type according to the classification by Small and Beckstead (1973). The above requirement of minimum cannabinoid ratios applies even when the total cannabinoid content is below 0.2% and thus cannabis is chemotype V (Mandolino and Carboni 2004). Lastly, for convenience, a maximum THC concentration of up to 1% includes all regional variation of light cannabis in this definition.

### 2.5.2 Cannabinoid composition of novel cannabinoid products and light cannabis

The current literature describes numerous problems associated with the unclear regulatory state of novel cannabinoid products as their exact composition is subject to unpredictable variability and often ambiguous. Novel cannabinoid products are commonly sold with statements that indicate they are not intended for consumption or introduce other disclaimers that enable them to remain in a regulatory grey area where it is difficult to identify a relevant legal framework for regulating them (Hughes et al. 2020). Thus, there are no measures in place for the regulatory bodies to control the composition of these products so their contents are not therefore effectively regulated or regularly monitored except for their THC content which must be low enough irrespective of the intended use of the products. In practice, the concentrations of cannabinoids in light cannabis vary greatly (Marchei et al. 2020, Nava et al. 2022) and even the measured THC concentrations can often be above the legal limits (Fabresse et al. 2023).

Additionally, the purity of extracted cannabinoids in products containing isolated cannabinoids and that of synthesized cannabinoids in SSC products is often not very high as impurities resulting from synthesis or unsuccessful separation during isolation are common. Subsequently, these products often contain inaccurately labelled levels of cannabinoids and THC

concentrations higher than the legal limit (Bonn-Miller et al. 2017, Roush and Hudalla 2021, Meehan-Atrash and Rahman 2022, Johnson 2021). Therefore, it is common for the actual composition of a given product to differ from the stated or expected composition and thus the product may not in actuality represent the type it might be designated to according to the categorization in section 2.5.1.

It is critical for the aims of this study to understand the cannabinoid composition of light cannabis. It could be assumed that the most likely cannabis plant chemotypes to be used in the production of low-THC cannabis products are III, IV and V as these typically have THC content that is low enough to comply with the regulations. Based on this assumption, Low-THC cannabis products, including light cannabis, likely contain CBD, CBG and often also THC as the most abundant cannabinoids by concentration. To elucidate this, literature reporting the composition of light cannabis samples needs to be summarized and the findings combined and analyzed to characterize the typical cannabinoid composition of light cannabis.

The cannabinoid composition of light cannabis flower samples has been investigated in a handful of studies. Marchei et al. (2020) analyzed THC and CBD concentrations in 12 different samples of dried hemp flowers sold as light cannabis in Italian hemp stores. Fabresse et al. (2023) analyzed cannabinoids in 39 samples acquired from shops in France between November 2021 and January 2022. Amendola et al. (2021) analyzed 31 samples from various cultivation areas in Italy and Nava et al. (2022) analyzed 24 samples of dried inflorescences sourced from industrial hemp farming agricultural cooperatives between April and June of 2022. The samples showed varying but low THC concentrations and generally higher CBD concentrations (Table 2). CBN concentrations were also reported by Nava et al. (2022) and Fabresse et al. (2023). It is also important to note that Marchei et al. (2020) measured each sample with both GC-MS and UHPLC-MS/MS methods. for convenience, only their GC-MS results were considered in this analysis, and they were chosen due to the reported THC concentrations being slightly higher for this method, representing the least favorable scenario from a hazard viewpoint. All the reported cannabinoid concentrations for the samples are included in appendix A of this thesis.

Table 2. Number of samples per study and the concentrations of THC and CBD in light cannabis samples.

| Study | Number of samples | THC% (range) | THC% (mean) | THC% (median) | CBD% (range) | CBD% (mean) | CBD% (median) |
|---|---|---|---|---|---|---|---|
| Marchei et al. (2020) | 12 | 0.31–0.39 | 0.22 | 0.21 | 2.2–8.2 | 4.35 | 4.4 |
| Fabresse et al. (2023) | 39 | 0.03–0.77 | 0.32 | 0.27 | 0.01–5.97 | 2.23 | 1.8 |
| Amendola et al. (2021) | 30 | 0.05–0.48 | 0.18 | 0.14 | 0.30–8.64 | 1.58 | 0.88 |
| Nava et al. (2022) | 24 | 0.08–0.42 | 0.24 | 0.25 | 1.05–8.78 | 4.39 | 4.1 |
| Total | 105 | 0.03–0.77 | 0.25 | 0.22 | 0.01–8.78 | 2.78 | 2.1 |

Though CBD:THC ratios were not included in any of these studies, they were calculated from the reported data using formula 1:

$$Sample\frac{CBD}{THC}ratio = \frac{sampleCBD\%}{SampleTHC\%}$$

When THC:CBD ratios were provided in the study, the corresponding CBD:THC ratios were determined using formula 2:

$$Sample\frac{CBD}{THC}ratio = \frac{1}{Sample\frac{THC}{CBD}ratio}$$

Additionally, to determine the total cannabinoid fraction which could be relevant for chemotype analysis, the sum of THC and CBD concentrations was used along with that of CBN, when available, to approximate the total cannabinoid content using formula 3:

$$Total\ fraction\ of\ cannabinoids\ (Cf\%) = Sample(THC\% + CBD\% + CBN\%)$$

These calculated values derived from the reported data are also included in appendix A of this thesis for reference.

CBD:THC ratios calculated for samples of Marchei et al. (2020) ranged between 6.9-28.1 with a mean of 20.8 while those of Fabresse et al. (2023) varied from 0.1 to 12.5 with a mean of 7.4 (Table 3). However, only two of the samples had CBD:THC ratios below 2 and one of these had a total cannabinoid fraction of 0.08% which was below 0.2% thus indicating chemotype V. Only one sample was Chemotype I, albeit with a very modest total cannabinoid concentration of 0.78%. CBD:THC ratios for Amendola et al. (2021) ranged from 2 to 24 with a mean of 9.0 whereas the ones for Nava et al. (2022) ranged from 2.5 to 67.5 with a mean of 22.4

Table 3. The calculated CBD:THC ratios and total cannabinoid fractions in light cannabis samples as well as the average concentrations of THC and CBD as milligrams per gram of light cannabis.

| Study | CBD:THC (range) | CBD:THC (mean) | Cf% (mean) | Cf% (median) | THC (mg/g) | CBD (mg/g) |
|---|---|---|---|---|---|---|
| Marchei et al. (2020) | 6.9–28.1 | 20.8 | 4.6 | 4.6 | 2.2 | 43.5 |
| Fabresse et al. (2023) | 0.1–12.5 | 7.4 | 2.6 | 2.2 | 3.2 | 22.3 |
| Amendola et al. (2021) | 2–24 | 9.0 | 1.8 | 1.1 | 1.8 | 15.8 |
| Nava et al. (2022) | 2.5–67.5 | 22.4 | 4.8 | 4.5 | 2.4 | 43.9 |
| Total | 0.01–67.5 | 12.8 | 3.1 | 2.4 | 2.5 | 27.8 |

In total, across the four studies, THC and CBD concentrations were reported for 105 samples with THC levels between 0.03% and 0.77%, a mean THC concentration of 0.25% and a median of 0.22% (Table 2). CBD concentrations ranged between 0.01-8.78% with a mean of 2.78% and a median of 2.1%. CBN concentrations were only reported by two of the studies, and thus available for only 68 of the samples and were generally very low with a mean of 0.06% and 0.3% being the highest level reported. CBD levels were not often particularly high despite the marketing claims surrounding light cannabis. However, the low CBD concentrations were primarily attributable to the low total cannabinoid concentrations that were below the median value of 2.4% for 50% of the samples (Table 3), closely corresponding to 50% of the samples with CBD concentration below 2.1% (Table 2). Indeed, when considering the even lower THC

concentrations, the CBD levels were, in fact, relatively high and the CBD:THC ratios for all samples had a mean of 12.8 and a median of 9.0. On average, one gram of light cannabis was determined to contain 2.5 mg of THC and about 28 mg of CBD (Table 3).

Nearly every sample was representative of the CBD-dominant chemotype III with only 2 samples being other chemotypes as mentioned above. 103 out of 105 or 98% of the samples met the definition of light cannabis established in section 2.5.1, while the remaining two samples had CBD:THC ratios below 2. Interestingly, the only chemotype I sample had lower THC concentration than many of the samples representing chemotype III, as if underscoring the complicated considerations of defining light cannabis. Lastly, an important consideration for characterizing cannabinoid mixtures in light cannabis is that the measured CBD:THC ratios were typically much higher than the definition threshold level of 2 and about 90% of the samples had CBD:THC ratios between 3 and 30 (Figure 4).

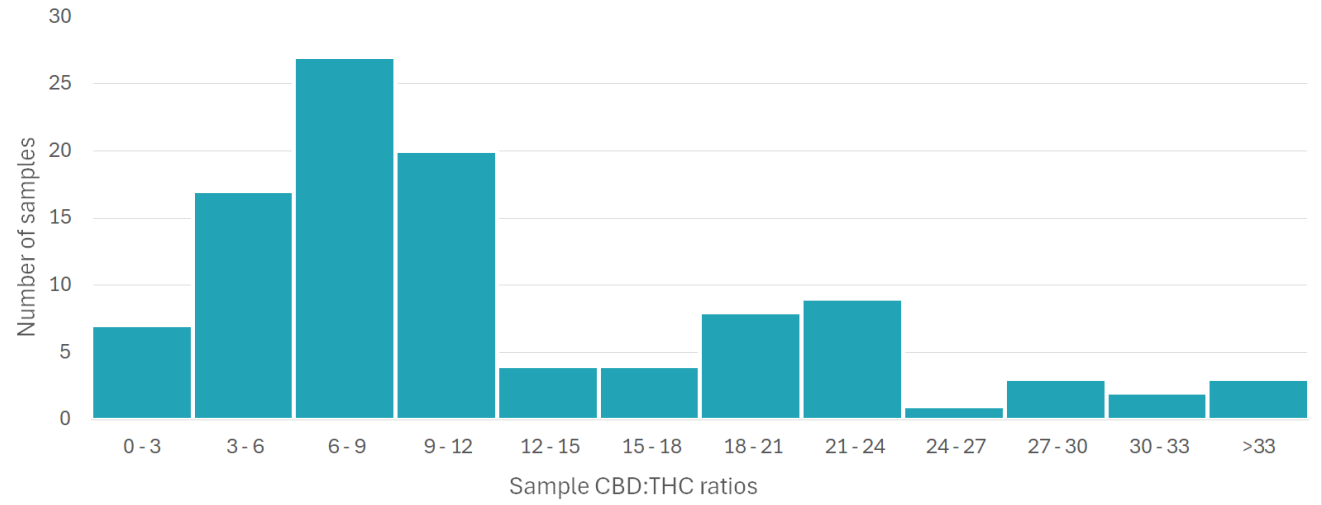


Figure 4. Distribution of different CBD:THC ratios in the light cannabis samples.

Almost all the samples analyzed in these studies could be identified as CBD-dominant light cannabis based on the available data. However, it is critical to note a key limitation in these studies, that the analyses were limited to two or three cannabinoids per sample and the presence of CBG, SSCs or many typical minor cannabinoids was not determined or quantified. Therefore, approximating the sample total cannabinoid concentration based on this data may

lead to underestimation even though CBD and THC can be expected to vastly dominate the sample cannabinoid spectrum. Additionally, there could be samples representing CBG-dominant strains or samples of SSC adulterated hemp containing HHC or other SSCs that would be misidentified as CBD-dominant in composition with these limited analyses. However, because of its recessive inheritance (de Meijer and Hammond 2005), the CBG-dominant chemotype requires special considerations for production and is therefore unlikely to have a very large market presence, especially when the CBD-dominant light cannabis is much more readily available for growing and easier to produce. Moreover, the samples were collected by June 2022 the latest (Nava et al. 2022), so SSCs adulteration of light cannabis was likely not yet widespread at the time as the first SSC identified in Europe, HHC, was only detected first time in May 2022 (Ujváry et al. 2023). It can therefore be assumed that despite the limited analyses of constituents, the data is likely mostly representative of the actual compositions and chemotypes of the samples.

One further study reporting composition for partially similar sample material has been published, but restrictions in their reporting prevented inclusion of their results in the summary above. Hädener et al. (2019) analyzed confiscated cannabis flower samples in Switzerland and from 531 total samples they categorized 205 as THC poor/CBD rich based on CBD:THC ratios of 3 or more. The median CBD concentration of these CBD-rich samples was 8.5% and the highest concentrations of CBD were 24.5%. THC concentrations had a median value of 0.3% and only 8 samples, corresponding to 4% of the CBD-rich samples, had THC concentrations exceeding 1% with the highest being 1.7% (Hädener et al. 2019). While their THC measurements were mostly in a similar range, their highest THC concentrations were two and CBD concentrations about three times as high as those in the findings summarized above. Most notably, their reported median CBD concentration was 4 times as high, being close to the highest concentration of 8.78% in the summary above, but this may be partially explained by their categorization of CBD-rich cannabis based on CBD:THC ratio of 3 in contrast to ratio of 2 used in this review. Also, the earlier legislation-prompted opportunity for establishing a market for light cannabis in Switzerland and the higher tolerated THC concentrations than in other regions may have enabled breeding and cultivation of more refined CBD-rich varieties compared to the largely industrial-hemp type varieties featured in the French and Italian data compiled above, possibly even suggesting a CBD

parallel to the trend of increasing THC concentrations in drug-type cannabis. Nevertheless, the findings of Hädener et al. (2019) corroborate the ones summarized above and indicate that quite similar high CBD:THC ratio mixtures are present in the Swiss light cannabis as well, although the CBD concentrations seem to be somewhat higher than elsewhere.

### 2.5.3 Light cannabis in human studies

A scarce number of studies investigating pharmacokinetic aspects, forensic diagnostics, and pharmacodynamic effects of light cannabis in humans has been published. These studies are of interest because they report pharmacodynamic- as well as blood pharmacokinetic measures which are useful for toxicological assessment (Table 4).

Pilot studies by Meier et al. (2018) and Hädener et al. (2019) investigated whether light cannabis smoking could elevate the whole blood THC concentrations high enough to produce a positive result in a confirmatory blood test after suspected driving under the influence and reported blood pharmacokinetic measures but no pharmacodynamic effects. A clinical trial by Pacifici et al. (2020) and Pichini et al. (2020) investigated cannabinoid concentrations in whole blood, oral fluid, urine and serum following light cannabis smoking to identify biomarkers for distinguishing its use from that of drug-type cannabis. They also reported pharmacodynamic measures, but found no changes in heart rate, blood pressure or body temperature and the only notable finding was that the participants were sleepy when returning home after the experiment. Lo Faro et al. (2023) performed a very similar clinical trial but measured a higher number of different cannabinoid metabolites in whole blood of the participants compared to the previous studies. However, pharmacodynamic measurements were not included in this study.

In their study, Pelletti et al. (2021) measured the psychomotor performance of participants after light cannabis smoking but reported that no significant effects were found in the assessments or reported by the participants. Studies by Spindle et al. (2020) and Bergeria et al. (2022), investigating pharmacodynamic effects and pharmacokinetic profiles of cannabinoids and their metabolites after vaporization and oral administration of CBD products and formulations, included interventions where CBD-dominant cannabis was vaporized by the participants. CBD-

dominant cannabis was reported to increase heart rate and to produce subjective effects in the participants but did not cause cognitive- or psychomotor impairment (Spindle et al. 2020).

The cannabis administered in these studies had CBD concentrations between 5.8% and 23.5% and THC concentrations that varied between 0.16% and 0.94% while the CBD:THC ratios ranged from 19.8 to 36.25. CBD doses of 42.7-100 mg and THC doses of 1.6-3.7 mg were administered in single exposure interventions whereas higher doses of 148.92-232 mg of CBD and 4.92-8.8 mg of THC were administered in single session multiple exposure interventions (Table 4). Meier et al. (2018) was the only study with an exposure period that was not confined to a single session and multiple doses were administered over 10 days totaling 680 mg of CBD and 32 mg of THC.

Table 4. The characteristics of studies investigating pharmacodynamics and blood pharmacokinetics following CBD-dominant light cannabis inhalation in humans.

| Study | Population | Type of cannabis | Route of exposure | Dose | Reported Pharmacodynamic effects |
|---|---|---|---|---|---|
| Meier et al. 2018 | One female volunteer, cannabis naïve before the single exposure experiment (n=1) | Single exposure experiment: 23.5% CBD, 0.94% THC (CBD:THC = 25) Repeated exposure experiment: 17% CBD, 0.8% THC (CBD:THC = 21.25) | Inhalation (smoking cannabis cigarettes) | Single exposure: 47 mg CBD + 1.9 mg THC.<br><br>Repeated exposure: 34 mg CBD + 1.6 mg THC twice daily for 10 days (Total 680 mg CBD + 32 mg THC.) | N/A |
| Hädener et al. 2019 | Healthy male subject (n=1) | 8.52% CBD, 0.43% THC<br><br>(CBD:THC = 19.8) | Inhalation (smoking cannabis cigarettes) | 1 cigarette: 42.7 mg CBD + 2.2 mg THC within 15 minutes<br><br>4 cigarettes: 170.8 mg CBD + 8.8 mg THC within 30 or 60 minutes | N/A |

| Study | Population | Type of cannabis | Route of exposure | Dose | Reported Pharmacodynamic effects |
|---|---|---|---|---|---|
| Pacifici et al. 2020 | One cigarette experiment (n=6), four cigarette experiment (n=6) | 5.8% CBD, 0.16% THC<br><br>(CBD:THC = 36.25) | Inhalation (smoking cannabis cigarettes) | 1 cigarette:<br>58 mg CBD + 1.6 mg THC within 1 hour<br><br>4 cigarettes:<br>232 mg CBD + 6.4mg THC within 4 hours | No significant changes in heart rate, blood pressure or body temperature. Sleepiness following repeated exposure session. |
| Pichini et al. 2020 Secondary report for Pacifici et al. (2020) | One cigarette experiment (n=6), four cigarette experiment (n=6) | 5.8% CBD, 0.16% THC<br><br>(CBD:THC = 36.25) | Inhalation (smoking cannabis cigarettes) | 1 cigarette:<br>58 mg CBD + 1.6 mg THC within 1 hour<br><br>4 cigarettes:<br>232 mg CBD + 6.4mg THC within 4 hours | No psychotropic effect was observed or reported |
| Spindle et al. 2020 | Healthy adult volunteers (n=18) | 10.5% CBD, 0.39% THC<br><br>(CBD:THC = 26.9) | Inhalation (vaporization) | 100 mg CBD + 3.7 mg THC, CBD-only 100 mg | Cannabis and CBD alone produced subjective effects and cannabis effects were rated higher than those of CBD alone. No cognitive or psychomotor impairment. |
| Bergeria et al. 2022 | Healthy adult volunteers (n=18) | 10.5% CBD, 0.39% THC<br><br>(CBD:THC = 26.9) | Inhalation (vaporization) | 100 mg CBD + 3.7 mg THC, CBD-only 100 mg | N/A |
| Pelletti et al. 2021 | Healthy young adults (n=18) | 12.41% CBD, 0.41% THC<br><br>(CBD:THC = 30.3) | Inhalation (smoking cannabis cigarettes) | 3 cigarettes:<br>148.92 mg CBD + 4.92 mg THC within 41.2-63 minutes | No significant effects on psychomotor performance and participants did not report feeling high after the experiment. |
| Lo Faro et al. 2023 | One cigarette experiment (n=6), four cigarette experiment (n=4) | 5.8% CBD, 0.16% THC<br><br>(CBD:THC = 36.25) | Inhalation (smoking cannabis cigarettes) | 1 cigarette:<br>58 mg CBD + 1.6 mg THC in 1 hour<br><br>4 cigarettes:<br>232 mg CBD + 6.4mg THC within 4 hours | N/A |

# 3 Aims of the study

Here the purpose and aims of this thesis are established. Choosing cannabis with high CBD:THC ratio has been included as a part of evidence-based lower-risk cannabis use guidelines (Fischer et al. 2017). The proposed role of CBD in attenuating the adverse effects of THC (Englund et al. 2017) should be especially evident in the context of light cannabis due to much higher CBD concentrations and CBD:THC ratios compared to drug-type cannabis. The purpose of this thesis is to determine whether the current literature supports this assumption. Aim of this study is to understand whether the presence of a high CBD level modifies the CNS effects of THC doses associated with light cannabis compared to cannabis with very little or no CBD. This would help to elucidate whether the hazard characteristics of light cannabis are different from regular drug-type cannabis so this could be considered in future risk assessments. Furthermore, because the route of administration has substantial impact on cannabinoid pharmacokinetics, its role in the possible CBD modulation of THC effects needs to be investigated. Lastly, Sub-chronic and chronic effects of light cannabis and similar CBD:THC mixtures are poorly researched. Identifying clinical studies of medical cannabis products high in CBD, suitable for elucidating CBD interaction with repeated exposure THC effects, could improve the understanding of these effects in the context of light cannabis consumption. The hypothesis tested is that CBD modulation attenuates the CNS effects of THC in mixtures with similar composition as those present light cannabis.

The research questions are formulated as follows:

-Does CBD modulate the acute subjective, cognitive, or psychological effects of THC at the CBD:THC ratios typical for light cannabis, when light cannabis or similar mixtures with CBD and THC are inhaled or orally ingested?
-What is the relevance of these findings at the dose levels typical of recreational use of light cannabis and does the high CBD:THC ratio in light cannabis change the hazard characteristics of light cannabis compared to drug-type cannabis?
-secondary: Does the route of administration matter for the modulatory effect of CBD and how?
-secondary: Is there evidence of CBD modulatory effects associated with sub-chronic or chronic exposures to light cannabis or similar mixtures with high CBD:THC ratios?

# 4 Materials and methods

In this chapter, the methods used for answering the research questions are presented in detail. A systematic review of literature was conducted to answer the research question whether CBD modulates the acute effects of THC at the CBD:THC ratios typical for light cannabis. PubMed database was searched using a systematic search strategy and the eligible articles were identified by predetermined inclusion/exclusion criteria. The eligible studies were included in a qualitative synthesis of their results.

## 4.1 PICO and inclusion/exclusion criteria

Implementing the recommendations of PRISMA (Preferred Reporting Items for Systematic review and Meta-Analysis) methodology guidelines (Page et al. 2021), PICO-framework (Population, Intervention, Comparator, Outcome) was used to specify the study characteristics determining the inclusion and exclusion criteria for study eligibility to be included in the qualitative synthesis (Table 5).

In general, studies investigating the effects of cannabis on cognition and psychiatric disease are notoriously affected by multiple confounding factors. For example, many users would be unlikely to limit their cannabis use to CBD-dominant cannabis only or be able to reliably characterize the type of cannabis they consume. Therefore, simultaneous use of prevalent high potency THC-dominant cannabis would likely confound the findings of any case-control, observational or cross-sectional studies focusing on CBD-dominant cannabis. Interventional studies enable control over many of these issues and better inference of causality (Englund et al. 2017). Furthermore, contrasting interventions would best enable reliable distinction between THC effects and CBD-THC mixture effects and allow for identification of possible CBD modulation of the THC effects. Acute and subtle effects could also be best detected with test batteries most feasibly incorporated into interventional studies. Lastly, it was determined that the limited nature and heterogeneity of the study data rendered meta-analysis unfeasible. Acknowledging these considerations, qualitative synthesis based on interventional studies was chosen as the preferred method to answer the research questions.

Table 5. PICO strategy

| Criteria | Inclusion Criteria | Exclusion criteria | Primary Search Term |
|---|---|---|---|
| P (Population) | >Humans<br><br>>Adults 18+ years<br><br>>Healthy or clinical conditions that do not affect the cognitive or psychological state<br><br>>Any cannabis user status (non-, light, heavy-, etc.) | >*In vitro* or *in vivo* only<br><br>>Neurological-, mental health issues or medications potentially affecting cognitive or psychological state of the participants | >Cannabis users and patients receiving medical cannabis |
| I (Intervention) | >CBD + THC administration with CBD:THC dose ratio≥2 via the same route (inhalation or oral)<br><br>>Or CBD-dominant cannabis with CBD:THC ratio≥2 administered via inhalation or oral route | >THC + CBD both not administered via the same route<br><br>>Route of administration not inhalation or oral<br><br>>Additional test compounds administered with THC + CBD or cannabis<br><br>>Doses of administered CBD or THC are not specified | >Inhalation and oral intake of THC and CBD |
| C (Comparison) | >CBD + THC at one or multiple different doses<br><br>>THC-only administration(s) at the same or equivalent dose(s) as the THC dose in CBD + THC co-administration(s) or CBD-dominant cannabis administration(s) | >Study does not include THC-only administration<br><br>>Dose of THC not the same or equivalent for THC-only and other treatment(s) | >Cognitive effects of THC and CBD co-administration |
| O (Outcome) | >CBD co-administration effects on subjective-, cognitive- (Memory, attention, learning, etc.) and psychological (anxiety, psychotomimetic symptoms) effects of THC | > No relevant outcomes reported | >Subjective, cognitive and psychological effects of cannabis |

The search was limited to human studies with the entire study population or at least one individually analyzed subgroup consisting of adult participants with at least 18 years of age and without existing medical conditions that could affect their cognitive or psychological state. Cannabis user status of the participants was not limited in any way. Complete health of the participants was not deemed a necessary requirement as studies involving medical cannabis interventions could provide information about the effects of sub-chronic or chronic exposures. Exclusion criteria related to study populations were that the study (1.) was *in vitro* or *in vivo* study only with no human participants and (2.) had participants with medical conditions that involved significant cognitive or psychological symptoms, frequent comorbidity associated with these symptoms or medications potentially introducing clinically relevant cognitive or psychological effects that might interfere with the relevant study outcomes.

Interventional studies investigating simultaneous administration of CBD and THC or administration of CBD-dominant cannabis via inhalation or oral route and comparing the CBD-THC mixture effects to the same or equivalent doses of THC alone, were deemed the most relevant to answering the research questions. THC-only doses were considered the same compared to THC-CBD mixtures when the same dose or dosage of THC was administered and equivalent whenever the delivery of the same dose of THC required justified adjustment of the administered dose and sound justification was provided. Additional requirement was that at least one intervention per study was required to have a minimum CBD:THC dose ratio of 2 which corresponds to the definition of light cannabis established in section 2.5.1. Exclusion criteria related to interventions were that (1.) THC and CBD were not both administered via the same route, (2.) the route of their administration was other than oral or inhalation, (3.) the study was limited to interventions where additional test compounds were administered during the same session as cannabinoids and (4.) the doses of administered cannabinoids were not specified on per participant basis as exact or weight-adjusted doses in mg, mg/kg or any unit that could be translated to mg or mg/kg per session or over a specified period of time and per participant basis. Additionally, exclusion criteria related to comparison were (1.) not including at least one intervention where only THC was administered and (2.) the administered doses of THC in THC-

only interventions were not the same or equivalent as the THC doses in THC-CBD mixture interventions within the same study.

Furthermore, studies were required to report effects in at least one of three domains of relevant outcomes - subjective, cognitive, or psychological effects. Subjective effects in this context referred to the intoxication and the altered state or experience induced by cannabinoids which could be assessed as participant-reported effects or with experimenter-reported objective assessments. Participant-reported effects referred to those measured with visual analog scales (VAS), Addiction Research Center Inventory (ARCI), Cannabis Experiences Questionnaire (CEQ), Marijuana Rating Form (MRF) or similar. Objective assessments of the altered mental state of the participants included experimenter observation- or interview-based assessments, such as Clinician Administered Dissociative States Scale (CADSS) or similar, that are not explicitly intended for measuring anxiety- or psychotic-like symptoms-related psychological effects. Cognitive effects relevant to this systematic review were those related to various aspects of cognition such as memory, attention as well as learning and assessed with any relevant behavioral tests measuring participant performance. Lastly, the relevant psychological effects were limited to those related to anxiety, paranoia or psychotomimetic symptoms and measured with State Trait Anxiety Inventory (STAI), Psychotomimetic States Inventory (PSI), Brief Psychiatric Rating Scale (BPRS), Positive and Negative Syndrome Scale (PANSS) or similar. Absence of any relevant outcomes reported in a study was established as the only exclusion criterion related to outcomes.

## 4.2 Systematic search strategy

Based on the PICO-statement and some additional considerations such as the surmised existence of eligible medical cannabis studies, a search query was developed for systematic literature search with the assistance of a library information specialist Laitinen H. The complete search query is included in Appendix B. MEDLINE database was searched via PubMed without restrictions on the publishing date but limiting the search to include articles in English language only and omitting reviews, meta-analyses, editorials, letters, conference papers, proceedings or

other articles with no original data. Literature search was performed on 7 March 2024 and the search query retrieved 965 articles. These articles were screened for eligibility for inclusion and additional eligible studies were then identified by screening the references of the included articles as well as the database-listed articles that have cited the included articles. Finally, after identifying all the relevant articles, the database lists of citing articles were simultaneously retrieved once more on 30.3.2024. These lists were compared to the previously retrieved ones and any recently added citing articles were identified and screened on this date, but no new eligible articles were identified. Therefore, the results of screening these lists were determined valid on this date.

## 4.3 Screening

Zotero citation management software was used to store, remove duplicates from, and screen the lists of articles acquired by exporting the results of the systematic search query as well as by exporting the lists of database-listed citing articles. Reference lists of the eligible included articles were screened by hand for additional eligible studies. Based on their titles and abstracts and according to the inclusion and exclusion criteria defined above, articles were either excluded or included for a full-text review. Articles deemed eligible for a full-text review were obtained as full-text copies and then screened according to the inclusion and exclusion criteria. Articles deemed eligible for inclusion after the full-text review were included in the systematic review for quality assessment and qualitative synthesis.

## 4.4 Quality assessment

Quality of the included articles was assessed using the National Heart, Lung, and Blood Institute (NHLBI) study quality assessment tools. All the chosen articles were evaluated under the Quality Assessment of Controlled Intervention Studies (NHLBI 2021). This quality assessment tool consists of 14 criteria that are yes or no questions but, for example, in the absence of adequate reporting can be determined as “cannot determine”, “not reported” or “not applicable.” The tool can be used to help appraise the quality of studies as good, fair, or poor depending on their risk

of bias. However, the tool is not intended or designed for determining an exact score and then rating the quality based on that, but rather to guide the researcher to consider various key areas of study execution and reporting for weaknesses or omissions that can contribute to risk of bias.

A guidance document provided along with the tool was used to help with the interpretation of applying the criteria. Vast majority of the included studies involved single-administration interventions and mostly utilized within-subject crossover designs, where participants switched between groups after each session. In contrast, many criteria of the tool have emphasis on longer-running clinical trials with parallel treatment groups. These considerations were thereby given less weight when using the tool to appraise the included studies and the items best suited for identifying the types of bias and confounding most likely present in these types of trials were prioritized in the assessment.

Based on the types of the included studies, some weighting adjustments for the criteria and deviations from guidelines of the guidance document were necessary: For the crossover studies, criterion 6. “Were the groups similar at baseline on important characteristics that could affect outcomes (e.g., demographics, risk factors, co-morbid conditions)?” was given less emphasis as each participant was their own control and comparison. For the same reason, criterion 8. “Was the differential drop-out rate (between treatment groups) at endpoint 15 percentage points or lower?” was often not applicable and thus estimation of attrition bias was based only on the criterion 7. “Was the overall drop-out rate from the study at endpoint 20% or lower of the number allocated to treatment?”

Furthermore, for all the studies, criterion 9. “Was there high adherence to the intervention protocols for each treatment group?” was interpreted in the context of uniform administration and delivery of the study compounds between participants in each session and criterion 10. “Were other interventions avoided or similar in the groups (e.g., similar background treatments)?” was primarily evaluated based on the study restrictions and controlling for participant adherence to avoiding the use of the investigated compounds prior to- or between

the interventions, and possible carryover effects that might interfere with measurements of the relevant outcomes.

When several reports were based on the same study, it was typical for the secondary reports to refer to the primary ones for reporting some of the study details (Hall et al. 2024, Oliver et al. 2024). These were therefore initially given the same rating as the primary reports and then criteria 11. "Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?", 13. "Were outcomes reported or subgroups analyzed prespecified (i.e., identified before analyses were conducted)?" and 14. "Were all randomized participants analyzed in the group to which they were originally assigned, i.e., did they use an intention-to-treat analysis?" were considered again in the context of the secondary report details to determine whether a change of the quality rating was warranted. The full list of criteria included in the NHLBI study quality assessment tool of controlled intervention studies is included in Appendix C.

## 4.5 Data extraction

Various data were extracted from each of the eligible studies. The extracted data consisted of:

- study type
- study characteristics (groups, group sizes, drop-outs)
- participants (number, sex, age)
- possible subgroups for the participants
- the routes of administration
- the types of material (purified cannabinoids or plant matrix, vehicle used)
- doses of CBD and THC for each intervention as well as the use of placebo control
- CBD:THC ratios
- the dosing regimens including simultaneous or delayed administration of compounds.
- the tests or assessments used
- the measured or assessed effects for subjective, cognitive, and psychological outcomes and the qualitative or quantitative findings of each test or assessment

- p-values of the relevant contrasts (baseline or placebo vs. THC, baseline or placebo vs. CBD and THC, THC vs. CBD and THC) for each relevant test or assessment

The data was primarily extracted from the reported data or supplementary materials. However, any necessary data unavailable in written or tabulated form but included in figures, was estimated with DigitizeIt-software for extraction.

## 4.6 Data Processing

For the findings that showed statistically significant differences between the THC and the CBD-THC mixture interventions, the effect sizes for THC effect relative to placebo or baseline, and for mixture effect relative to THC effect were calculated with formulae 4 and 5.

The difference in outcomes attributable to THC effect with Formula 4:

$$THC\ effect\ size\ relative\ to\ placebo/baseline\ (\%) = \frac{THC\ value - placebo/baseline\ value}{THC\ value} * 100\ (\%)$$

The difference between THC and mixture outcomes with Formula 5:

$$Mixture\ effect\ size\ relative\ to\ THC\ (\%) = \frac{Mixture\ value - THC\ value}{THC\ value} * 100\ (\%)$$

Finally, the potential size of CBD modulatory effect was calculated using formula 6:

$$CBD\ modulation\ effect\ size\ (\%) = \frac{Mixture\ effect\ size\ relative\ to\ THC\ (\%)}{THC\ effect\ size\ relative\ to\ placebo/baseline\ (\%)} * 100\ (\%)$$

Lastly, it is of note that as opposed to the best practice of performing parallel screening, quality assessment and data extraction by multiple individuals, suggested by the PRISMA guidelines to avoid risk of bias, these steps were performed by a single individual.

# 5 Results

With the systematic search query, a total of 965 records were extracted from PubMed. Due to confining the search to a single database, no duplicates were identified or removed. 945 records were excluded following title and abstract screening and of the 20 full-text-screened articles, 15 were excluded due to: unspecified administered THC and CBD doses (n=1), lack of simultaneous THC-CBD administration (n=2), lack of THC-only administration (n=1), invalid route of administration (n=1), too low CBD:THC ratio (n=4), THC-only dose different from CBD-THC mixture THC dose (n=3), including participants under 18 years old and no adult-only groups for separate analysis (n=1) and lack of relevant outcomes reported (n=2). Screening the references and the citing articles of the full-text-screened eligible articles (n=5) revealed seven eligible articles and in total 12 articles were included in a qualitative synthesis (Figure 5). List of the excluded full-text-screened articles and reasons for their exclusion are included in Appendix D.

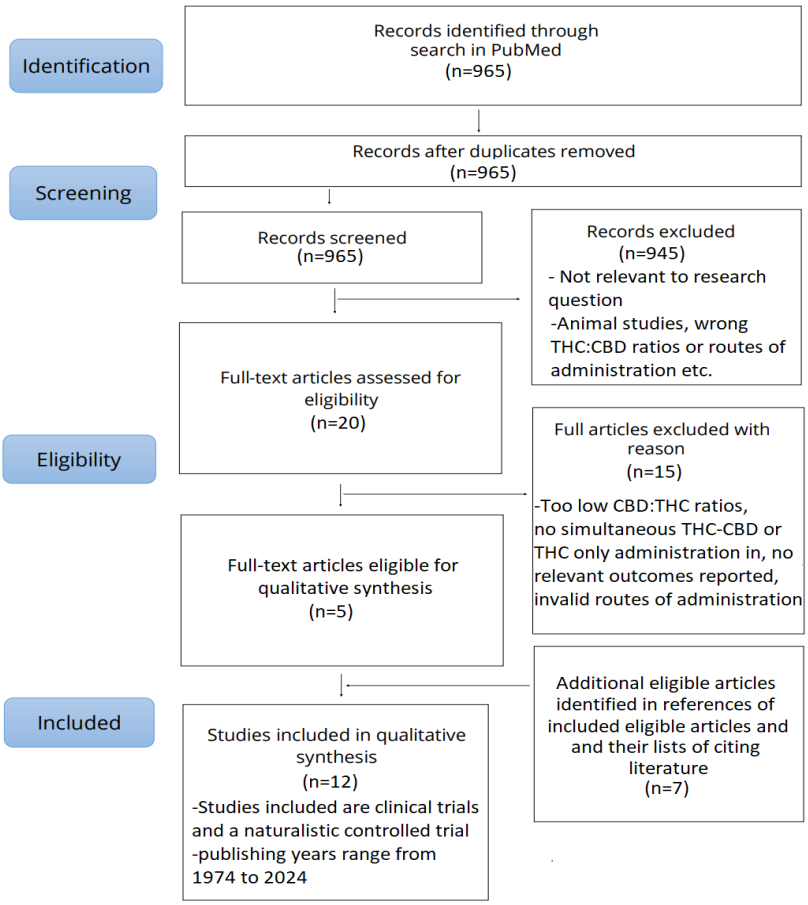


Figure 5. Flowchart of article screening and selection process.

## 5.1 Articles eligible for qualitative synthesis

The 12 articles eligible for inclusion were relevant to answering the research questions. The studies contrasted interventions with THC and CBD-THC mixtures of varying ratios and reported effects on subjective, cognitive, and psychological outcomes in adult humans. The studies were primarily reports of clinical trials (n=11) but one was a report of a naturalistic study (n=1) (Table 6).

11 reports of eight separate clinical trials, of which six were of crossover design, were included (Table 6). Six of the reports were based on three studies with two reports each. Morgan et al. (2018) report was based on same study as that of Hindocha et al. (2015), Oliver et al. (2024) reported secondary outcomes of same study as Englund et al. (2023) and reports by Lawn et al. (2023) and Hall et al. (2024) were based on a single study as well. The remaining six articles were reports corresponding to separate studies (Karniol et al. 1974, Hollister and Gillespie 1975, Dalton et al. 1976, Zuardi et al. 1982, Woelfi et al. 2020, Sainz-Cort et al. 2021). The eight clinical trials had study population sizes that varied between 8 and 64 participants with a total of 264 adult participants between the ages 18 and 50. One of the studies had separate subgroups of adolescents aged 16-17 years and adults aged 26-29 years (Lawn et al. 2023, Hall et al. 2024) but the adolescent subgroup results were not considered in this systematic review. Some results with combined data from adolescent and adult subgroups were considered suitable for adult-only interpretation in the qualitative synthesis when statistical analysis showed no significant effect of age group on the results. Results were analyzed for multiple subgroups in two other crossover design trials as well: one stratifying some results by participant schizotypal traits and cannabis user status (Hindocha et al. 2015, Morgan et al. 2018) and other by Dalton et al. (1976) involving groups with either simultaneous CBD and THC inhalation or CBD-pretreatment 30 minutes prior to THC inhalation.

One naturalistic intervention study with a crossover design was included as well (Sainz-Cort et al. 2021). The study compared the effects of high dose THC inhalation with a similar dose of THC in CBD-THC mixture administered in a cannabis social club setting. The participants had no direct researcher interaction and attended online meetings with the researchers during the

intervention sessions for interviews and outcome assessments. The 20 participants of this study were 21 years or older (Table 6).

Table 6. The articles eligible for inclusion as well as their study types and demographics.

| Reference (Year) | Study type | Number of participants (Drop-outs) | Treatment group size | Gender | Participant age in years | Separately analyzed subgroups |
|---|---|---|---|---|---|---|
| Karniol et al. (1974) | Clinical trial | 40 | 5 | M: 40<br>F: 0 | 21–34 | Placebo group,<br>3 CBD-only groups,<br>1 THC-only group,<br>3 CBD+THC groups |
| Hollister and Gillespie (1975) | Clinical trial (Crossover) | 15 | 15 | M: 15<br>F: 0 | 18+ | - |
| Dalton et al. (1976) | Clinical trial (Crossover) | 24 (1) | 15 (CBD+THC simultaneously)<br>8 (CBD pretreatment) | M: 24<br>F: 0 | 21–24 | Simultaneous treatment group, Pretreatment group |
| Zuardi et al. (1982) | Clinical trial (Crossover) | 8 | 8 | M: 6<br>F: 2 | 20–38 | - |
| Hindocha et al. (2015) | Clinical trial (Crossover) | 48 | 12 | M: 34<br>F: 14 | 21 (sd: 2.13)<br>22.9 (sd: 2.02)<br>21.42 (sd:1.62)<br>21.5 (sd: 1.38) | Light cannabis use + low schizotypy, Light cannabis use + high schizotypy, Heavy cannabis use + low schizotypy, Heavy cannabis use + high schizotypy |
| Morgan et al. (2018) Secondary outcomes for Hindocha et al. (2015) | Clinical trial (Crossover) | 48 | 12 | M: 34<br>F: 14 | 21 (sd: 2.13)<br>22.9 (sd: 2.02)<br>21.42 (sd:1.62)<br>21.5 (sd: 1.38) | Light cannabis use + low schizotypy, Light cannabis use + high schizotypy, Heavy cannabis use + low schizotypy, Heavy cannabis use + high schizotypy |

| Reference (Year) | Study type | Number of participants (Drop-outs) | Treatment group size | Gender | Participant age in years | Separately analyzed subgroups |
|---|---|---|---|---|---|---|
| Woelfi et al. (2020) | Clinical trial | 61 (1) | 15 | M: 61<br>F: 0 | 19–36 | Placebo group, CBD-only group, THC-only group, CBD+THC group |
| Sainz-Cort et al. (2021) | Naturalistic study (Crossover) | 20 (2) | 18 | M: 8<br>F: 10 | 29.94 (sd: 6.92)<br><br>Minimum age 21 | - |
| Englund et al. (2023) | Clinical trial (Crossover) | 64 (18) | 46 | M: 25<br>F: 21 | 21–50 | - |
| Lawn et al. (2023) | Clinical trial (Crossover) | 59<br>(11) | 24 (Adolescents)<br><br>24 (Adults) | M: 12<br>F: 12<br><br>M: 12<br>F: 12 | 16–17<br><br>26–29 | Adolescent group, adult group |
| Hall et al. (2024) Secondary outcomes for Lawn et al. (2023) | Clinical trial (Crossover) | 59<br>(11) | 24 (Adolescents)<br><br>24 (Adults) | M: 12<br>F: 12<br><br>M: 12<br>F: 12 | 16–17<br><br>26–29 | Adolescent group, adult group |
| Oliver et al. (2024) Secondary outcomes for Englund et al. (2023) | Clinical trial (Crossover) | 64 (18) | 46 | M: 25<br>F: 21 | 21–50 | - |

## 5.2 Quality assessment results

The National Heart, Lung, and Blood Institute (NHLBI) quality assessment tools were used to rate the articles included in this review. Half the articles were rated poor due to serious limitations in reporting or methodology and a high risk of bias. Four articles were rated fair and only two were considered good. Both articles with good quality ratings were based on the same study by Lawn et al. (2023) and Hall et al. (2024) (Table 7).

Table 7. Summary of quality assessment for the included articles.

| Reference (year) | Study type | NHLBI quality assessment tool | Comments |
|---|---|---|---|
| Karniol et al. (1974) | Clinical trial | Poor | 5/14 criteria met.<br>Measurement bias possible due to methodology. Interindividual differences were not controlled adequately and combined with small group sizes caused an increased risk of bias. Concentrations of study compounds likely exceeded solubility in the dosing vehicle. |
| Hollister and Gillesipie (1975) | Clinical trial | Poor | 5/14 criteria met.<br>Randomization or blinding were not indicated. Missing reporting on many details, while not indicative of bias, precludes excluding the risk of bias. |
| Dalton et al. (1976) | Clinical trial | Fair | 8/14 criteria met.<br>Randomization was not clearly indicated.<br>Performance bias possible |
| Zuardi et al. (1982) | Clinical trial | Poor | 6/14 criteria met.<br>Performance bias possible. Study had very low power compared to the more recent ones designed to measure the estimated effect sizes of THC-CBD interaction. Concentrations of study compounds likely exceeded solubility in the dosing vehicle. |
| Hindocha et al. (2015) | Clinical trial | Fair | 9/14 criteria met.<br>Randomization was not adequately reported.<br>Performance bias possible. |

| Reference (year) | Study type | NHLBI quality assessment tool | Comments |
|---|---|---|---|
| Morgan et al. (2018) Secondary report on the same study as Hindocha et al. (2015) | Clinical trial | Fair | 9/14 criteria met. Randomization was not adequately reported. Performance bias possible. |
| Woelfi et al. (2020) | Clinical trial | Fair | 12/14 criteria met. Mostly eligible for good rating, but design was likely inadequate to control the effect of interindividual variation. Restricted subject weight bracket and male-only limitation may have introduced bias. |
| Sainz-Cort et al. (2021) | Naturalistic study | Poor | 9/14 criteria met. A combination of inadequate control of confounders, potentially unreliable delivery of intervention drugs and subjective self-reported measures resulted in high risk of bias. |
| Englund et al. (2023) | Clinical trial | Poor | 10/14 criteria met. Methodologically sound and comprehensively reported study but exclusion of 18/65 (~28%) randomized participants represented a fatal flaw introducing high risk of attrition bias. |
| Lawn et al. (2023) | Clinical trial | Good | 12/14 criteria met. Methodologically sound and comprehensively reported study with rather high rate of withdrawal (19%), but mostly unrelated to study drugs or protocol. Slight risk of carryover effect. |
| Hall et al. (2024) Secondary report on the same study as Lawn et al. (2023) | Clinical trial | Good | 12/14 criteria met. Methodologically sound and comprehensively reported study with rather high rate of withdrawal (19%), but mostly unrelated to study drugs or protocol. Slight risk of carryover effect. |
| Oliver et al. (2024) Secondary report on the same study as Englund et al (2023) | Clinical trial | Poor | 10/14 criteria met. Methodologically sound and comprehensively reported study but exclusion of 18/65 (~28%) randomized participants represented a fatal flaw introducing high risk of attrition bias. |

## 5.3 Study interventions

Eight of the included articles reported on inhalation studies while the remaining four reported on studies that employed the oral route of administration (Table 8). The doses of THC administered via inhalation ranged between 1.9 mg and 65 mg, when the weight-adjusted doses were calculated for a 75-kg person. However, apart from the study by Sainz-Cort et al. (2021), all the inhalation studies utilized THC doses of only 10 mg or less. CBD:THC ratios of mixtures used in these interventions were between 1:1 and 6:1, but all the studies included at least one intervention with a ratio of 2:1 or higher.

Table 8. Characteristics of interventions in the included studies.

| Reference (Year) | Placebo (or baseline) | CBD - only | Delay between CBD and THC | Doses of THC alone and THC + CBD in mixture(s) | CBD:THC ratio(s) | Matrix | Route of administration |
|---|---|---|---|---|---|---|---|
| Dalton et al. (1976) | Yes | Yes | No/Yes<br>(30 min) | THC 25 µg/kg,<br>THC 25 µg/kg + CBD 150 µg/kg | 0:1, 6:1 | Extracted blank cannabis spiked with purified THC or CBD | Inhalation (Cigarette smoking) |
| Hindocha et al. (2015) | Yes | Yes | No | THC 8 mg,<br>THC 8mg + CBD 16 mg | 0:1, 2:1 | Purified THC and CBD in ethanol | Inhalation (vaporization) |
| Morgan et al. (2018)<br>Secondary outcomes for Hindocha et al. (2015) | Yes | Yes | No | THC 8 mg,<br>THC 8mg + CBD 16 mg | 0:1, 2:1 | Purified THC and CBD in ethanol | Inhalation (vaporization) |
| Sainz-Cort et al. (2021) | Yes | Yes | No | THC 65 mg,<br>THC 65 mg + CBD 130 mg (100 + 325 mg of extract) | 0:1, 2:1 | THC dominant full-spectrum extract and CBD dominant full-spectrum extract | Inhalation (vaporization) |

| Reference (Year) | Placebo (or baseline) | CBD - only | Delay between CBD and THC | Doses of THC alone and THC + CBD in mixture(s) | CBD:THC ratio(s) | Matrix | Route of administration |
|---|---|---|---|---|---|---|---|
| Englund et al. (2023) | Yes (baseline) | No | No | THC 10 mg,<br>THC 10 mg + CBD 10 mg, 20 mg or 30 mg | 0:1, 1:1, 2:1, 3:1 | THC-dominant (Bedrocan) and CBD-dominant (Bedrolite) cannabis | Inhalation (vaporization) |
| Lawn et al. (2023) | Yes | No | No | THC 0.107 mg/ kg,<br>THC 0.107 mg/kg + CBD 0.320 mg/ kg | 0:1, 3:1 | Bedrocan and Bedrolite cannabis | Inhalation (vaporization) |
| Hall et al. (2024) Secondary outcomes for Lawn et al. (2023) | Yes | No | No | THC 0.107 mg/ kg,<br>THC 0.107 mg/kg + CBD 0.320 mg/ kg | 0:1, 3:1 | Bedrocan and Bedrolite cannabis | Inhalation (vaporization) |
| Oliver et al. (2024) Secondary outcomes for Englund et al. (2023) | Yes (baseline) | No | No | THC 10 mg,<br>THC 10 mg + CBD 10 mg, 20 mg or 30 mg | 0:1, 1:1, 2:1, 3:1 | Bedrocan and Bedrolite cannabis | Inhalation (vaporization) |
| Karniol et al. (1974) | Yes | Yes | No | THC 30 mg,<br>THC 30 mg + CBD 15 mg, 30mg or 60 mg | 0:1, 1:2, 1:1, 2:1 | Purified THC and CBD in orange juice | Oral |
| Hollister and Gillespie (1975) | No | No | No | THC 20 mg,<br>THC 20 mg + CBD 40 mg | 0:1, 2:1 | Purified THC and CBD in food. "Extracted marihuana placebo" added to THC | Oral |
| Zuardi et al. (1982) | Yes | Yes | No | THC 0.5 mg/kg,<br>THC 0.5 mg/kg + CBD 1.0 mg/kg | 0:1, 2:1 | Purified THC and CBD in artificial lemon juice | Oral |
| Woelfi et al. (2020) | Yes | Yes | Yes<br>(30 min) | THC 20 mg,<br>THC 20 mg + CBD 800 mg | 0:1, 40:1 | Purified THC and CBD | Oral |

The oral studies utilized somewhat higher doses of THC in general, ranging between 20 mg and 37.5 mg, when the weight-adjusted doses were calculated for a 75-kg person. CBD:THC ratios of the mixtures used in these interventions ranged from 1:2 to 40:1. However, the highest administered ratio was only 2:1 in three of these four studies (Karniol et al. 1974, Hollister and Gillespie 1975, Zuardi et al. 1982) (Table 8). Most of these studies involved simultaneous administration of cannabinoids in a mixture. However, Dalton et al. (1976) reported no modulatory effect for CBD inhaled 30 minutes prior to THC and Woelfi et al. (2020) administered oral CBD 30 minutes prior to THC and reported similarly negative findings.

## 5.4 CBD modulation of study outcomes

The included studies reported outcomes related to subjective, cognitive, and psychological effects of THC and CBD-THC mixtures. Significant differences between placebo or baseline and THC-only intervention findings suggested that THC-related impairment or effect was seen in that outcome under study conditions. Furthermore, statistically significant differences between the THC-only- and CBD-THC mixture intervention outcomes could be interpreted to suggest that CBD modulation of these THC effects might explain the differences between THC and mixture.

### 5.4.1 Subjective effects

10 out of the 12 included articles reported subjective outcomes for THC and CBD-THC mixture effects and six of these articles showed some degree of evidence of CBD modulating the subjective effects of THC (Table 9). Karniol et al. (1974) reported a higher intensity of experimenter-observed reactions in the THC-only-treated participants compared to the mixture-treated ones. The median rating of intensity was 4 for THC and 2 for the mixture suggesting a 50% reduction by CBD modulation (Table 10). Hollister and Gillespie (1975) reported a CBD-related increase in duration and intensity of THC effects measured with a rating of peak intensity, and Addiction Research Center Inventory (ARCI)-questionnaires. However, these results were only qualitative due to the absence of statistical analysis or placebo comparison. Dalton et al. (1976) reported a decrease in number of symptoms following mixture inhalation compared to

THC alone as indicated by fewer answered questions in Cornell Medical Index-questionnaire at 35 minutes and at 55 minutes after administration. Lower intensity of subjective high was also associated with the mixture as suggested by lower rating of psychological high at 0 minutes after administration when the ratings for THC and mixture were 5.3 and 4.3 and at 15 minutes when they were 5.7 and 4.5, respectively. In both assessments, the results showed a 22-41% reduction in effects associated with CBD. Zuardi et al. (1982) interviewed participants for descriptive summaries of effects and the qualitative results showed markedly diminished effects of oral THC when combined with CBD in 2:1 ratio (Table 10). Additionally, ARCI-questionnaire produced a significantly higher "most homogenous group"-rating for THC effects compared to the mixture at 18.357 and 9.643 points, respectively, suggesting potential CBD modulation by -47%. Sainz-Cort et al. (2021) reported significantly lower scores for mixture compared to THC alone in several Visual Analogue Scales (VAS) assessments that suggested a CBD modulatory effect of 66-108%, but not in VAS assessments of feelings of appetite or hunger (Table 10). Lastly, a VAS assessment of "feel drug effect" showed significant differences at 20-180 minutes after administration with a 12% increase associated with mixture CBD, but no significant difference in effects at the 20 minutes timepoint alone (Lawn et al. 2023).

Table 9. Subjective outcomes reported by the included articles, comparison of the effects associated with THC and CBD-THC mixture and suggested modulation of the THC effects by CBD.

| Measurements or assessments | Reference (year) | Subcategory of subjective measure | Statistical significance (effect direction) THC vs. Placebo | Statistical significance (effect direction) CBD vs. THC | CBD modulation of relevant THC effect |
|---|---|---|---|---|---|
| Addiction research center inventory (ARCI) - hallucinogen | Hollister and Gillespie (1975) | Participant-reported | NR | NR | Yes (Qualitative) |
| Addiction research center inventory (ARCI) - marihuana | Hollister and Gillespie (1975) | Participant-reported | NR | NR | Yes (Qualitative) |
| Addiction research center inventory (ARCI) - marihuana | Zuardi et al. (1982) | Participant-reported | +(↑) [a] | +(↓) | Yes |

| Measurements or assessments | Reference (year) | Subcategory of subjective measure | Statistical significance (effect direction) THC vs. Placebo | Statistical significance (effect direction) CBD vs. THC | CBD modulation of relevant THC effect |
|---|---|---|---|---|---|
| Addiction research center inventory -18 item | Sainz-Cort et al. (2021) | Participant-reported | +(↑) | - | No |
| Adjective mood rating scale (EWL) | Woelfi et al. (2020) | Participant-reported | - | - | No |
| Cornell medical index (CMI) | Dalton et al. (1976) | Participant-reported | +(↑) | +(↓) | Yes |
| Descriptive summary of interviews and reports | Zuardi et al. (1982) | Experimenter-reported objective | NR | NR | Yes (Qualitative) |
| Picture-rating task | Oliver et al. (2024) | Participant-reported | - [a] | - | No |
| Pleasurable responses | Englund et al. (2023) | Participant-reported | +(↑) [a] | - | No |
| Psychological effects | Karniol et al. (1974) | Experimenter-reported objective | +(↑) | +(↓) | Yes |
| Psychologic high rating | Dalton et al. (1976) | Participant-reported | +(↑) | +(↓) | Yes |
| Rating of peak intensity | Hollister and Gillespie (1975) | Participant-reported | NR | NR | Yes (Qualitative) |
| Scale of bodily symptoms | Zuardi et al. (1982) | Participant-reported | - | NR | No |
| Subjective feelings self-rating scale | Zuardi et al. (1982) | Participant-reported | +(↑) | NR | No |
| Visual analogue scales (VAS) | Hindocha et al. (2015) | Participant-reported | +(↑) | - | No |
| Visual analogue scales (VAS) | Sainz-Cort et al. (2021) | Participant-reported | +(↑) | +(↓) | Yes |
| Visual analogue scales (VAS) | Englund et al. (2023) | Participant-reported | +(↑) [a] | - | No |
| Visual analogue scales (VAS) | Lawn et al. (2023) | Participant-reported | +(↑) | +(↑) | Yes |

a Comparison THC vs. baseline. NR= not reported.

Table 10. Reported values and calculated percentual effect sizes for the subjective outcomes with suggested CBD modulation of THC effects. Statistical significance is indicated by asterisk (*).

| Reference (year) | Measurement | Placebo or baseline | THC | CBD+THC | Effect size (%) THC vs. placebo | Effect size (%) THC vs. placebo | Effect size (%) CBD modula-tion |
|---|---|---|---|---|---|---|---|
| Karniol et al. (1974) | Psychological reaction group - median | 0 | 4 | 2 | 100 | -50 * | -50 |
| Hollister and Gillespie (1975) | Peak intensity | NR | 6.7 | 7.0 | NR | 4.5 | NR |
| Hollister and Gillespie (1975) | ARCI-hallucinogen 2h | NR | 6.0 | 6.6 | NR | 10 | NR |
| Hollister and Gillespie (1975) | ARCI-hallucinogen 4h | NR | 4.5 | 6.0 | NR | 33 | NR |
| Hollister and Gillespie (1975) | ARCI-marihuana 2h | NR | 7.3 | 7.3 | NR | 0 | NR |
| Hollister and Gillespie (1975) | ARCI-marihuana 4h | NR | 7.0 | 8.0 | NR | 14 | NR |
| Dalton et al. (1976) | CMI questions 0 min - mean (pooled SD) | 4.7 (4.0) | 14.1 (4.0) | 11.1 (4.0) | 67 * | -21 | -32 |

| Reference (year) | Measurement | Placebo or baseline | THC | CBD+THC | Effect size (%) THC vs. placebo | Effect size (%) THC vs. placebo | Effect size (%) CBD modula-tion |
|---|---|---|---|---|---|---|---|
| Dalton et al. (1976) | CMI questions 15 min - mean (pooled SD) | 4.4 (4.8) | 13.7 (4.8) | 11.1 (4.8) | 68 * | -19 | -28 |
| Dalton et al. (1976) | CMI questions 35 min - mean (pooled SD) | 3.1 (4.8) | 13.7 (4.8) | 10.3 (4.8) | 77 * | -25 * | -32 |
| Dalton et al. (1976) | CMI questions 55 min - mean (pooled SD) | 2.9 (4.8) | 11.1 (4.8) | 7.7 (4.8) | 74 * | -31 * | -41 |
| Dalton et al. (1976) | CMI questions 75 min - mean (pooled SD) | 3.0 (4.5) | 9.5 (4.5) | 6.7 (4.5) | 68 * | -29 | -43 |
| Dalton et al. (1976) | CMI questions 95 min - mean (pooled SD) | 3.1 (4.3) | 7.5 (4.3) | 5.9 (4.3) | 59 * | -21 | -36 |
| Dalton et al. (1976) | high rating 0 min - mean (pooled SD) | 0.7 (1.6) | 5.3 (1.6) | 4.3 (1.6) | 87 * | -19 * | -22 |
| Dalton et al. (1976) | high rating 15 min - mean (pooled SD) | 0.9 (1.7) | 5.7 (1.7) | 4.5 (1.7) | 84 * | -21 * | -25 |
| Dalton et al. (1976) | high rating 35 min - mean (pooled SD) | 0.9 (1.8) | 5.1 (1.8) | 3.9 (1.8) | 82 * | -24 | -29 |
| Dalton et al. (1976) | high rating 55 min - mean (pooled SD) | 0.5 (1.6) | 3.6 (1.6) | 3.1 (1.6) | 86 * | -14 | -16 |
| Dalton et al. (1976) | high rating 75 min - mean (pooled SD) | 0.3 (1.4) | 2.7 (1.4) | 2.1 (1.4) | 88 * | -22 | -25 |
| Dalton et al. (1976) | high rating 95 min - mean (pooled SD) | 0.3 (0.9) | 1.7 (0.9) | 1.2 (0.9) | 82 * | -29 | -36 |

| Reference (year) | Measurement | Placebo or baseline | THC | CBD+THC | Effect size (%) THC vs. placebo | Effect size (%) THC vs. placebo | Effect size (%) CBD modula-tion |
|---|---|---|---|---|---|---|---|
| Zuardi et al. (1982) | Interview reports - descriptive summary 0-30 min (number of participants affected) | Sleepiness (2) | Difficulty in concentrating (5)<br>Depersonalization (3)<br>Dizziness (3)<br>Change in body image (2)<br>Paresthesia (2)<br>Dry mouth (2)<br>Restlesness (2) | Sleepiness (2) | NR | NR | NR |
| Zuardi et al. (1982) | Interview reports - descriptive summary 30-60 min (number of participants affected) | Sleep (3) | Difficulty in concentrating (5)<br>Anxiety (5)<br>Hiperacusia (5)<br>Depersonalization (4)<br>Sleep (4)<br>Change in body image (3)<br>Resistance to communication (3)<br>Dizziness (3)<br>Dry mouth (3)<br>Disconnected thoughts (2)<br>Change in perception of time (2)<br>Nausea (2) | Sleep (4) | NR | NR | NR |
| Zuardi et al. (1982) | Interview reports - descriptive summary 60-120 min (number of participants affected) | Sleep (5) | Hiperacusia (5)<br>Sleep (5)<br>Difficulty in concentrating (4)<br>Resistance to communication (3)<br>Change in body image (2)<br>Disconnected thoughts (2)<br>Anxiety (2)<br>Visions of colored geometric forms with the eyes closed (2)<br>Paranoid ideas (2)<br>Dizziness (2)<br>A sensation of cold (2) | Sleep (7)<br>Difficulty in concentrating (3)<br>Depersonalization (2)<br>Paresthesia (2) | NR | NR | NR |

| Reference (year) | Measurement | Placebo or baseline | THC | CBD+THC | Effect size (%) THC vs. placebo | Effect size (%) THC vs. placebo | Effect size (%) CBD modula-tion |
|---|---|---|---|---|---|---|---|
| Zuardi et al. (1982) | ARCI-Ma (most homogenous group) | - | 18.357 | 9.643 | 100 * | -47 * | -47 |
| Sainz-Cort et al. (2021) | VAS - Time perception - mean (sd) | 23.69 (38.97) | 156.12 (102.30) | 68.43 (59.12) | 85 * | -56 * | -66 |
| Sainz-Cort et al. (2021) | VAS - Change in control of thoughts - mean (sd) | 24.54 (43.42) | 164.07 (99.04) | 69.65 (79.61) | 85 * | -58 * | -68 |
| Sainz-Cort et al. (2021) | VAS - Feeling high - mean (sd) | 16.72 (30.88) | 210.68 (104.92) | 75.83 (73.20) | 92 * | -64 * | -70 |
| Sainz-Cort et al. (2021) | VAS - Feeling drowzy - mean (sd) | 30.35 (35.65) | 85.35 (72.09) | 31.056 (24.73) | 64 * | -64 * | -99 |
| Sainz-Cort et al. (2021) | VAS - Feeling muzzy - mean (sd) | 9.49 (24.39) | 88.44 (76.94) | 20.92 (26.53) | 89 * | -76 * | -86 |
| Sainz-Cort et al. (2021) | VAS - Feeling dreamy - mean (sd) | 20.49 (41.24) | 84.67 (90.50) | 36.80 (48.35) | 76 * | -57 * | -75 |
| Sainz-Cort et al. (2021) | VAS - Mental slowness - mean (sd) | 20.01 (33.53) | 119.29 (93.73) | 52.60 (57.66) | 83 * | -56 * | -67 |
| Sainz-Cort et al. (2021) | VAS - Hearing voices - mean (sd) | 0.42 (1.77) | 17.08 (40.35) | 0.00 (0) | 98 | -100 * | -103 |
| Sainz-Cort et al. (2021) | VAS - Special meaning - mean (sd) | 10.01 (24.35) | 61.29 (68.40) | 27.11 (50.12) | 84 * | -56 * | -67 |
| Sainz-Cort et al. (2021) | VAS - Suspicious ideas or beliefs - mean (sd) | 2.78 (10.23) | 20.39 (36.99) | 1.39 (3.89) | 86 * | -93 * | -108 |

| Reference (year) | Measurement | Placebo or baseline | THC | CBD+THC | Effect size (%) THC vs. placebo | Effect size (%) THC vs. placebo | Effect size (%) CBD modula-tion |
|---|---|---|---|---|---|---|---|
| Sainz-Cort et al. (2021) | VAS - Feelings of appetite - mean (sd) | 29.21 (51.94) | 55.32 (68.24) | 34.24 (58) | 47 * | -38 | -81 |
| Sainz-Cort et al. (2021) | VAS - Feelings of hunger - mean (sd) | 22.54 (40.87) | 47.06 (61.13) | 31.22 (49.77) | 52 | -34 | -65 |
| Lawn et al. (2023) | VAS - Feel drug effect (20 min only) - (MD) (95%CI) | 6.292 (5.343, 7.240) [a] | 6.813 (5.964, 7.661) [b] | 0.521 (-0.121, 1.163) [c] | 100 * [d] | 8.3 | 8.3 |
| Lawn et al. (2023) | VAS - Feel drug effect (20min-180min) - (MD) | 4.552 [a] | 5.12 [b] | 0.568 [c] | 100 * [d] | 12 * [d] | +12 |

a Combined data for adult and adolescent groups. Mean difference is calculated THC vs. placebo.

b Combined data for adult and adolescent groups. Mean difference is calculated CBD+THC vs. placebo.

c Combined data for adult and adolescent groups. Mean difference is calculated CBD+THC vs. THC.

d Significance is calculated for combined adult and adolescent data, but age*drug p>0.05 indicates no effect of age on the results, so the data is assumed valid for adult-only interpretation. NR = not reported.

### 5.4.2 Cognitive effects

Eight of the 12 included articles reported cognitive outcomes for THC and CBD-THC mixture effects and two of these articles showed some degree of evidence of CBD modulating the cognitive effects of THC (Table 11).

According to Karniol et al. (1974) CBD-THC mixture produced significantly smaller impairments compared to THC in a time production task measuring time perception. THC alone caused more impairment than 2:1 CBD-THC mixture in estimating 60 second intervals without feedback at 45 minutes after ingestion with a mean of 33.6 (SE=2.1) seconds compared to 50.0 (SE=1.4) seconds, respectively. At 95 minutes, the mean estimations were 39.6 (SE=2.1) and 54.7 (SE=1.5) seconds and at 180 minutes 39.3 (SE=2.5) and 56.9 (SE=2.4) seconds, respectively. These results

suggested a 66-103% reduction in the THC effects associated with CBD. Feedback improved both THC and mixture associated impairment at all time points, but the difference between them remained significant (Table 12). Hindocha et al. (2015) investigated effects of THC and CBD on facial affect recognition with an emotional processing task. THC caused significant impairment at 40% intensity of probe images, lowering the recognition accuracy to 39.75% (SD=4.51%) while the 2:1 CBD-THC mixture results of 43.52% (SD=10.9) were comparable to 44.9% (SEM=1.55) of placebo. The difference between effects of THC and CBD-THC mixture suggested CBD-associated modulation by 73%.

Table 11. Cognitive outcomes reported by the included articles, comparison of the effects associated with THC and CBD-THC mixture and suggested modulation of the THC effects by CBD.

| Measurements or assessments | Reference (year) | Subcategory of cognitive measure | Statistical significance (effect direction) THC vs. placebo | Statistical significance (effect direction) THC+CBD vs. THC | CBD modulation of relevant THC effect |
|---|---|---|---|---|---|
| Attentional bias task | Hall et al. (2024) | Attentional bias | - | - | No |
| Attentional bias task | Oliver et al. (2024) | Attentional bias | +(↑) [a] | - | No |
| Emotional processing task | Hindocha et al. (2015) | Facial affect recognition | +(↓) | +(↑) | Yes |
| d2 Test of attention | Woelfi et al. (2020) | Concentration and attention | - | - | No |
| Fluency | Morgan et al. (2018) | Phonological and semantic fluency | - | NR | No |
| Reitan's trailmaking test | Morgan et al. (2018) | Processing speed | - | NR | No |
| Digit symbol coding task | Woelfi et al. (2020) | Processing speed | - | - | No |
| Time production task | Karniol et al. (1974) | Time perception | +(↓) | +(↑) | Yes |
| Hopkins verbal learning task (HVLT-R) | Englund et al. (2023) | Verbal learning and memory | +(↓) [a] | - | No |

| Measurements or assessments | Reference (year) | Subcategory of cognitive measure | Statistical significance (effect direction) THC vs. placebo | Statistical significance (effect direction) THC+CBD vs. THC | CBD modulation of relevant THC effect |
|---|---|---|---|---|---|
| Prose recall | Morgan et al. (2018) | Verbal episodic memory | +(↓) | NR | No |
| Prose recall | Lawn et al. (2023) | Verbal episodic memory | +(↓) | - | No |
| Forward and reverse digit span | Englund et al. (2023) | Working memory and attention | +(↓) [a] | - | No |
| Letter-number-sequencing test | Woelfi et al. (2020) | Working memory | - | - | No |
| Spatial N-back | Morgan et al. (2018) | Working memory | +(↓) | NR | No |
| Spatial N-back | Englund et al. (2023) | Working memory | - [a] | - | No |

a Comparison THC vs. baseline. NR= not reported.

Table 12. Reported values and calculated percentual effect sizes for the cognitive outcomes with suggested CBD modulation of THC effects. Statistical significance is indicated by asterisk (*).

| Reference (year) | Measurement | Placebo or baseline | THC | CBD+THC | Effect size (%) THC vs. placebo | Effect size (%) THC vs. placebo | Effect size (%) CBD modula-tion |
|---|---|---|---|---|---|---|---|
| Karniol et al. (1974) | Time production without feedback T1 (baseline) - mean(SE) | 58.3 (3.1) | 58.3 (3.1) | 58.3 (3.1) | 0 | 0 | 0 |
| Karniol et al. (1974) | Time production with feedback T2 (baseline) - mean(SE) | 59.8 (2.1) | 59.8 (2.1) | 59.8 (2.1) | 0 | 0 | 0 |
| Karniol et al. (1974) | Time production without feedback T3 (45 min) - mean(SE) | 58.3 (1.0) | 33.6 (2.1) | 50.0 (1.4) | 74 * | 49 * | -66 |

| Reference (year) | Measurement | Placebo or baseline | THC | CBD+THC | Effect size (%) THC vs. placebo | Effect size (%) THC vs. placebo | Effect size (%) CBD modula-tion |
|---|---|---|---|---|---|---|---|
| Karniol et al. (1974) | Time production with feedback T4 (45 min) - mean(SE) | 59.6 (0.6) | 40.2 (2.6) | 58.4 (1.7) | 48 * | 45 * | -94 |
| Karniol et al. (1974) | Time production without feedback T5 (95 min) - mean(SE) | 59.4 (0.7) | 39.6 (2.1) | 54.7 (1.5) | 50 * | 38 * | -76 |
| Karniol et al. (1974) | Time production with feedback T6 (95 min) - mean(SE) | 59.6 (0.7) | 49.2 (3.3) | 59.9 (2.2) | 21 * | 21 * | -103 |
| Karniol et al. (1974) | Time production without feedback T7 (180 min) - mean(SE) | 57.8 (1.4) | 39.3 (2.5) | 56.9 (2.4) | 47 * | 45 * | -95 |
| Karniol et al. (1974) | Time production with feedback T8 (180 min) - mean(SE) | 59.9 (0.6) | 51.0 (2.7) | 57.9 (1.2) | 17 * | 14 * | -78 |
| Hindocha et al. (2015) | Affect recognition 20% - Accuracy % mean (SEM) | 11.6 (0.75) [a] | 13.9 (1.0) [a] | 13.0 (0.85) [a] | 17 | -6,5 | -39 |
| Hindocha et al. (2015) | Affect recognition 40% - Accuracy % mean (SEM) | 44.9 (1.55) [a] | 39.75 (SD=4.51) [b] | 43.52 (SD=10.9) [b] | 13 * | 9,5 * | -73 |
| Hindocha et al. (2015) | Affect recognition 60% - Accuracy % mean (SEM) | 72 (1.7) [a] | 73.1 (1.75) [a] | 71.0 (1.7) [a] | 1,5 | -2,9 | -191 |
| Hindocha et al. (2015) | Affect recognition 80% - Accuracy % mean (SEM) | 76.9 (1.7) [a] | 77.9 (1.6) [a] | 75.4 (1.45) [a] | 1,3 | -3,2 | -250 |
| Hindocha et al. (2015) | Affect recognition 100% - Accuracy % mean (SEM) | 79.0 (1.0) [a] | 77.7 (1.0) [a] | 76.9 (1.05) [a] | 1,7 | -1 | 62 |

a Results are estimated from a figure with Digitize It-software.

b Results have standard deviation available instead of Standard error of mean

### 5.4.3 Psychological effects

Five of the 12 included articles reported psychological outcomes for THC and CBD-THC mixture effects and two of these articles showed some degree of evidence of CBD modulating the psychological effects of THC (Table 13).

Sainz-Cort et al. (2021) reported significant increases in several subscale scores of Psychotomimetic States Inventory (PSI) assessment of psychological effects to be associated with THC. Mixture caused significantly less impairment in the cognitive disorganization subscale of PSI with a score of 6.61 (SD=6.55) compared to the THC score of 13.78 (SD=8.43), suggesting a 70% decrease by CBD modulation (Table 14). According to Lawn et al. (2023) there were no significant differences in the total PSI scores between THC and CBD-THC mixture. However, pairwise comparison of the cognitive disorganization subscale of PSI scores for THC and mixture showed a significant mean difference of 1.896, suggesting that the mixture produced slightly more intense psychological effects compared to THC alone, corresponding to a CBD associated increase of 48%.

Table 13. Psychological outcomes reported by the included articles, comparison of the effects associated with THC and CBD-THC mixture and suggested modulation of the THC effects by CBD.

| Measurements or assessments | Reference (year) | Subcategory of cognitive measure | Statistical significance (effect direction) THC vs. placebo | Statistical significance (effect direction) THC+CBD vs. THC | CBD modulation of relevant THC effect |
|---|---|---|---|---|---|
| Brief psychiatric rating scale (BPRS) | Morgan et al. (2018) | Anxiety, psychotomimetic symptoms | +(↑) | NR | No |
| Community assessment of psychic experiences (CAPE-state) | Englund et al. (2023) | Psychotomimetic symptoms | +(↑) [a] | - | No |
| Positive and negative syndrome scale - Positive (PANSS-P) | Englund et al. (2023) | Psychotomimetic symptoms | +(↑) [a] | - | No |

| Measurements or assessments | Reference (year) | Subcategory of cognitive measure | Statistical significance (effect direction) THC vs. placebo | Statistical significance (effect direction) THC+CBD vs. THC | CBD modulation of relevant THC effect |
|---|---|---|---|---|---|
| Positive and negative syndrome scale (PANSS) | Lawn et al. (2023) | Psychotomimetic symptoms | +(↑) | - | No |
| Psychotomimetic states inventory (PSI) | Morgan et al. (2018) | Psychotomimetic symptoms | +(↑) | NR | No |
| Psychotomimetic states inventory (PSI) | Sainz-Cort et al. (2021) | Psychotomimetic symptoms | +(↑) | +(↓) | Yes |
| Psychotomimetic states inventory (PSI) | Englund et al. (2023) | Psychotomimetic symptoms | +(↑) [a] | - | No |
| Psychotomimetic states inventory (PSI) | Lawn et al. (2023) | Psychotomimetic symptoms | +(↑) | +(↑) | Yes |
| Spielbergs state-trait anxiety inventory (STAI) | Zuardi et al. (1982) | Anxiety | +(↑) [a] | NR | No |
| State social paranoia scale (SSPS) | Englund et al. (2023) | Psychotomimetic symptoms | - a | - | No |

a Comparison THC vs. baseline. NR = not reported

Table 14. Reported values and calculated percentual effect sizes for the psychological outcomes with suggested CBD modulation of THC effects. Statistical significance is indicated by asterisk (*).

| Reference (year) | Measurement | Placebo or baseline | THC | CBD+THC | Effect size (%) THC vs. placebo | Effect size (%) THC vs. placebo | Effect size (%) CBD modula-tion |
|---|---|---|---|---|---|---|---|
| Sainz-Cort et al. (2021) | PSI - Subscale - Delusional thinking - mean (SD) | 2.44 (3.47) | 4.39 (4.42) | 2.89 (3.89) | 44 * | -34 | -77 |
| Sainz-Cort et al. (2021) | PSI - Subscale - Perceptual distortion - mean (SD) | 2.22 (1.86) | 7.06 (4.92) | 4.11 (2.93) | 69 * | -42 | -61 |
| Sainz-Cort et al. (2021) | PSI - Subscale - Cognitive disorganization - mean (SD) | 3.56 (2.87) | 13.78 (8.43) | 6.61 (6.55) | 74 * | -52 * | -70 |

| Reference (year) | Measurement | Placebo or baseline | THC | CBD+THC | Effect size (%) THC vs. placebo | Effect size (%) THC vs. placebo | Effect size (%) CBD modula-tion |
|---|---|---|---|---|---|---|---|
| Sainz-Cort et al. (2021) | PSI - Subscale - Anhedonia - mean (SD) | 4.33 (3.01) | 5.72 (3.43) | 4.11 (4.30) | 24 | -28 | -116 |
| Sainz-Cort et al. (2021) | PSI - Subscale - Mania - mean (SD) | 4.06 (2.01) | 6.67 (3.18) | 5.33 (2.99) | 39 * | -20 | -51 |
| Sainz-Cort et al. (2021) | PSI - Subscale - Paranoia - mean (SD) | 0.56 (0.92) | 1.89 (1.78) | 1.06 (1.30) | 70 * | -44 | -62 |
| Lawn et al. (2023) | PSI - Total - MD (95%CI) | 7.771 (2.844, 12.698) [a] | 10.792 (6.172, 15.411) [b] | –3.021 (−6.954, 0.912) [c] | 100 * [d] | 39 | 39 |
| Lawn et al. (2023) | PSI-Cognitive disorganisation -MD | 3.938 [a] | 5.833 [b] | 1.896 [c] | 100 * [d] | 48 * [d] | +48 |
| Lawn et al. (2023) | PSI-Perceptual distortion-MD | 1.667 [a] | 2.146 [b] | 0.479 [c] | 100 * [d] | 29 | 29 |
| Lawn et al. (2023) | PSI-Paranoia-MD | 0.333 [a] | 0.625 [b] | 0.292 [c] | 100 | 88 | 88 |
| Lawn et al. (2023) | PSI-Mania-MD | 0.750 [a] | 1.250 [b] | 0.500 [c] | 100 | 67 | 67 |

a Combined data for adult and adolescent groups. Mean difference is calculated THC vs. placebo.

b Combined data for adult and adolescent groups. Mean difference is calculated CBD+THC vs. placebo.

c Combined data for adult and adolescent groups. Mean difference is calculated CBD+THC vs. THC

d Significance is calculated for combined adult and adolescent data, but age*drug p>0.05 indicates no effect of age on the results, so the data is assumed valid for adult-only interpretation.

All the available relevant data and statistics for the included studies are included in Appendix E.

# 6 Discussion

In the final chapter, the results of this thesis are discussed. The clinical significance as well as the relevance and implications of the results for evaluating hazard characteristics of light cannabis products are determined by a qualitative synthesis of the data. The findings are then discussed in detail and considerations for future research are outlined. Thereafter, the limitations of this study are considered, and conclusions are presented.

## 6.1 Characteristics of the included studies

The included studies investigated both inhalation and oral administration of THC and THC-CBD mixtures. While inhalation was investigated in eight of the studies, there were somewhat fewer that employed the oral route of administration, with only four studies. Study populations were somewhat small with the highest allocated number of participants in a single study being 64. However, small population sizes were often offset by the fact that the studies mostly utilized crossover designs, offering better statistical power with smaller populations and better control of interindividual variability due to every participant acting as their own control. The few studies that did not utilize a crossover design but had separate parallel treatment groups, seemed to consider demographics mostly in an adequate way and control for confounders such as previous drug use when allocating participants to different groups to ensure group similarity and comparability.

However, many of the studies were quite old and conducted in the 1970s and 1980s when the rigor of conducting and reporting of clinical studies was not up to modern standards, and this contributed to poor study quality in many cases. The newer studies were generally of better quality but still suffered some omissions and fatal flaws that needed to be considered when interpreting their results.

The outcomes were assessed using participant reports as well as researcher-administered assessments, both of which could be problematic. Retrospective subjective assessments could be affected by retrograde amnesic effects of THC and expert interpretation could be affected, for

example, by performance bias when the participants are noticeably intoxicated or sober after placebo. Large variability in the utilized assessments also complicated the between-study comparisons of many outcomes but, in general, the assessments seemed to be sensitive to THC effects. So, even though most of them had not been validated specifically for assessing or measuring the effects of cannabis, they seemed adequate for the purposes of these studies.

## 6.2 Clinical significance of THC effect modulation by CBD

Here the clinical significance of the findings is discussed. Clinical significance is indicated when a statistically significant result emerges from a true effect that could be attributed to the role of CBD and is likely not overtly confounded by other factors. Also, to be considered clinically significant, this effect should be sufficiently large to have practical relevance so that, for instance, it could feasibly be perceived as noticeable by participants. When the administered doses of THC are similar or equivalent for interventions with THC and CBD-THC mixtures, a statistically significant contrast between the intervention outcomes suggests a possibility that CBD modulates the effects of THC in the mixtures of the two via pharmacological interaction. However, the magnitude of these modulatory effects, study- and intervention details, as well as the consistency of results between studies and their quality need to be carefully weighed and analyzed by qualitative synthesis to determine the clinical significance of these findings. Conclusions based on the findings regarding CBD modulation are outlined for each category of outcomes and route of administration, answering the first primary research question.

### 6.2.1 Subjective effects

Heterogeneity of the subjective effects assessments used in the earlier studies hampers between-study comparison of the subjective effect results. However, apart from Woelfi et al. (2020), who utilized a modernized EWL-60 Adjective Mood Rating Scale, the newer studies starting from Hindocha et al. (2015) utilized similar VAS assessments for subjective effects assessment and thus their results have better between-study comparability. Overall, the assessments used appeared valid and reliable for the use of assessing the effects of cannabis.

Cannabinoid Inhalation studies of Dalton et al. (1976), Sainz-Cort et al, (2021) and Lawn et al. (2023) reported that CBD-THC mixtures produced subjective effects that were significantly different from the subjective effects of THC alone.

Lawn et al. (2023) was rated as the highest quality study among the inhalation studies, with a sufficiently large population, good methodology as well as thorough reporting and reported a modestly higher VAS score of “feel drug effect” over all timepoints associated with 3:1 CBD-THC mixture compared to THC with a mean difference of 0.568 between the mixture and THC alone. However, this value was relatively modest compared to the mean differences between cannabinoid and placebo conditions at 4.552 and 5.12 for THC and mixture, respectively, amounting to a CBD modulatory effect of 12%. Moreover, VAS score for “feel drug effect” was not different between THC and mixture at the 20-minute timepoint alone, when the intensity of effects could be expected to be near their peak and furthermore, none of the six other VAS scores showed any differences between these interventions. Considering this data, while it is possible that slightly higher subjective intensity of effects was associated with CBD, the magnitude of this modulation was somewhat slight and likely not clinically significant.

In contrast, Sainz-Cort et al. (2021) reported that THC alone compared to 2:1 mixture produced significantly higher ratings of subjective effects by a large absolute margin in multiple VAS assessments, suggesting a modulatory effect of CBD ranging between 66% and 103%. The 65 mg administered dose of THC was very high compared to the other inhalation studies that utilized doses of 10 mg or less and these results could therefore suggest that higher doses of THC, but not lower doses, produce subjective effects intense enough to be amenable to attenuation by CBD co-administration. The mixture CBD dose at 130 mg was also much higher than those utilized in the other inhalation studies which could suggest that higher inhaled doses of CBD are required for the modulatory effects to occur. However, in this study, resin with total mass of 100 mg and 425 mg for the THC and mixture interventions, respectively, was vaporized at 210°C for delivery utilizing a Storz & Bickel GmbH & Co. Volcano Medic vaporizer. An article by Solowij et al. (2014) about the development of a protocol for delivery of CBD-THC mixtures by vaporization for clinical studies utilizing similar Volcano vaporizer device, described difficulties in using this

apparatus for delivery of high doses of cannabinoids. They reported that a load exceeding 200 mg caused substantial decreases in the delivered doses due to suspected saturation effects, even at a temperature of 230°C, which was reported to produce much better performance compared to 210°C. Additionally, Solowij et al. (2014) reported simultaneous vaporization of large doses of CBD decreasing the relative proportion of delivered THC. Because the amount of resin for the mixture intervention at 425 mg was more than twice as much as the highest dose determined feasible to be delivered by a more refined protocol, it is quite possible that far lower THC doses than intended were delivered to the participants by Sainz-Cort et al. (2021), resulting in lower ratings in VAS assessments for mixture compared to THC alone. Despite this, it cannot be completely ruled out that this difference could be at least partially due to CBD since the 130 mg dose was much higher than in the other included inhalation studies with CBD doses of up to only 30 mg. Further, better-controlled studies utilizing similarly high CBD doses would be needed to refute or ascertain these findings.

Dalton et al. (1976) study participants reportedly experienced a larger number of symptoms and higher subjective intensity following THC-only inhalation compared to CBD-THC mixture. While these differences seem rather modest with about 25-30% reduction in the number of symptoms, corresponding to CBD modulation by 32-41% and a difference of 1-1.2 points on a 10-point scale for intensity with a corresponding modulatory effect size of 22-25%, the differences may be sufficiently large to represent a true effect. This could suggest that increasing the CBD:THC ratio to 6:1 is enough to produce a slight decrease in the subjective effects of inhaled THC. However, at 25 µg/kg, the dose of administered THC was quite low, about 1.9 mg for a 75-kg person. The article was also slightly ambiguous about whether the dose they reported referred to an administered dose or a delivered dose with an estimated 50 % availability. Therefore, allowing this latter interpretation, the administered dose could have been closer to 4 mg for a 75-kg person. Even this dose would have been somewhat low, and it seems questionable whether this would have produced robust enough subjective THC effects to allow the assessments to have sufficient sensitivity to detect any CBD modulatory effects. For instance, Kleinloog et al. (2014) demonstrated that 2 mg of inhaled THC produced only threshold subjective effects and at 4 mg the effects were much less consistent than at 8 mg. Moreover, Dalton et al. (1976) did not report

controlling the dose delivery with any protocol and the irritating properties of inhaled cannabinoids, which are discussed in more depth below, might have resulted in suppressed delivery of cannabinoids in the mixture group. While it is possible that these results showed a true CBD modulatory effect, these modest differences could also be explained by insufficient sensitivity of methodology or group differences in dose delivery. Furthermore, it also seems unlikely that the relatively small differences in low-dose THC effects between treatments would have been noticeable to the participants, so it is doubtful that these results were clinically significant. Thereby this evidence of CBD modulatory effect is of low-quality.

Of the four studies that employed the oral route of administration, Woelfi et al. (2020) was of highest quality, with the largest population size, the best controlled conditions, and thorough reporting. Their findings did not support CBD modulation of THC subjective effects, even at a very high 40:1 CBD to THC ratio and rather large doses of 20mg THC and 800 mg CBD. Even the relatively large 20 mg oral dose of THC did not produce significant changes compared to placebo in the EWL-60 assessment. This assessment has been previously used to assess the effects of psilocybin, ketamine and MDMA (Studerus et al. 2010), but is possibly not very sensitive to THC which could explain the absence of significant effects in this case. While the THC dose was insufficient to produce significant subjective effects, the trend level effects of THC were not significantly different from the mixture effects which in turn were significantly different from placebo. Overall, THC and CBD-THC mixture produced very similar subjective effects in this study.

The results of Woelfi et al. (2020) are in striking contrast to the previous studies with oral dosing that have consistently reported remarkable differences in subjective effects between the THC- and mixture treated participants (Karniol et al. 1974, Hollister and Gillespie 1975, Zuardi et al. 1982). While these results could be interpreted to imply that higher THC doses, of up to 40 mg in case of Zuardi et al. (1982), produced more pronounced effects and thus increased sensitivity to modulatory action by CBD, even at lower ratios, it is quite possible that these results did not reflect clinically significant effects of CBD. These studies were of poor quality, had very small group sizes and at least Karniol et al. (1974) study was very susceptible to confounding arising

from interindividual differences as it did not utilize a crossover design. However, such pronounced differences between treatments are not likely solely attributable to within-subject variability or small group sizes since such high doses of THC can be expected to be consistently very intoxicating, especially since the participants in these studies were reported to not use cannabis regularly and thus were unlikely have tolerance for THC.

The large variation in subjective effects between the treatments could, however, arise due to misclassification bias. Both Karniol et al. (1974) and Zuardi et al. (1982) administered the cannabinoids dissolved in water-based drinks of orange juice and artificial lemon juice, respectively. High doses of CBD and THC, which are poorly soluble in hydrophilic liquids, were likely to reach saturation concentrations and get deposited on the container surface or any organic material suspended in the solution, as both cannabinoids competed for the same, and quite limited, solvation capacity of the non-lipophilic solvent. Both studies dissolved the administered doses to volumes of 200 ml of their respective juice vehicles with combined cannabinoid concentrations reaching 0.375 - 0.6 mg/ml. These concentrations were unlikely to remain dissolved in solution as CBD and THC have reported water solubility values of 0.0126 mg/l and 0.00263 mg/ml (Drugbank Online), respectively. Therefore, the reported differences between THC and mixture effects in these studies were most likely largely attributable to inadvertent and unnoticed differences in the delivered THC doses between interventions rather than CBD modulation of the THC effects. Hollister and Gillespie (1975) did not report any statistical analysis or -significance in their article. Therefore, while their results are supportive of CBD modulation of THC effects, albeit in the opposite direction than those of Karniol et al. (1974) and Zuardi et al. (1982), they cannot be given much weight as evidence.

The conclusion based on all the above findings is that CBD does not seem to modulate the subjective effects of THC associated with inhaled mixtures at ratios of 2:1 or 3:1, but here is scarce low-quality evidence that CBD may slightly attenuate the subjective effects of THC at high CBD:THC ratio of 6:1. This lack of modulatory effects may be due to low doses of only up to 30 mg of CBD in these interventions, not due to the low ratios alone. Low-quality evidence also suggests that modulation attenuating the subjective effects could occur at a high inhaled CBD

dose of 130 mg, even when the mixture ratio is as low as 2:1. However, CBD does not seem to elicit clinically significant modulation of the subjective effects of THC associated with orally ingested CBD-THC mixtures.

### 6.2.2 Cognitive effects

The included studies showed very little evidence supporting CBD modulation of the cognitive effects of THC. The cognitive assessments used were largely not validated specifically for determining cannabinoid effects, but some of them appeared to detect THC intoxication consistently and reliably at the utilized doses and therefore could be assumed suitable for use in these studies. Cognitive outcomes related to information processing were impaired by inhaling THC in the studies of Morgan et al. (2018), Englund et al. (2023) and Hall et al. (2023) that reported negative effects on verbal learning and memory as well as working memory. In contrast, oral THC at 20 mg did not produce significant effects on cognitive outcomes related to information processing (Woelfi et al. 2020). None of these THC effects showed any sign of possible modulation by CBD. However, some other cognitive outcomes suggested modulatory effects by CBD (Karniol et al. 1974, Hindocha et al. 2015).

Attentional bias was affected by THC in a study by Oliver et al. (2024) but this was not observed by Hall et al. (2024). This effect was not modulated by CBD in either study. Time perception (Karniol et al. 1974) and emotional processing (Hindocha et al. 2015) were both impaired by THC and a statistically significant improvement was seen associated with CBD co-administration in both studies. As stated above, Karniol et al. (1974) was susceptible to suspected bias due to inconsistent delivery of the study cannabinoids because of an incompatible vehicle. Improvements in time perception associated with CBD co-administration were thereby most likely attributable to lower-than-intended delivered doses of THC. Hindocha et al. (2015) reported that CBD attenuated THC impairment in affect recognition at 40% intensity of expression and that CBD-THC mixture effects were no different from placebo. Because of the small absolute differences between treatments, this improvement was about 10% of the absolute score and thus relatively modest, even though this suggested a CBD modulatory effect of 73%. However, CBD alone improved affect recognition at 60% intensity with a moderate effect

size of partial eta squared = 0.137 when CBD was contrasted against placebo and trend-level improvement was also seen associated with CBD at 80% and 100% intensity as well. This suggests the possibility that CBD had an independent, enhancing effect on emotional processing, which could offset the impairment caused by THC. While relatively small, the independent CBD effect on this outcome suggests a true CBD effect modulating the cognitive effects of THC on emotional processing. However, the very small absolute differences of up to 10% between treatments may not be sufficient to be noticeable by the participants and thus the CBD modulatory effect on emotional processing is unlikely to be clinically significant.

CBD in inhaled CBD-THC mixtures does not seem to acutely modulate the effects of THC on the cognitive processes that are related to information processing and important for learning as well as educational attainment. Similarly, there is no effect on attentional bias related to the cognitive aspects of addiction development. However, there is scarce, intermediate-quality evidence, supporting CBD modulation of THC effects on emotional processing at CBD-THC mixture ratio of 2:1, producing slight attenuation of this effect. Because none of the oral studies reported statistically significant changes in cognitive outcomes associated with THC or mixture, there is insufficient evidence to determine whether CBD modulates the cognitive effects of orally ingested CBD-THC mixtures.

### 6.2.3 Psychological effects

The included studies showed very little evidence supporting CBD modulation of the psychological effects of THC. Only some of the assessments used were validated specifically for determining cannabinoid effects, but most of them appeared to detect THC intoxication consistently and reliably at the utilized doses and therefore could be assumed suitable for use in these studies. Inhaled THC and CBD-THC mixtures were associated with anxiety and psychotomimetic symptoms (Morgan et al. 2018, Sainz-Cort et al. 2021, Englund et al. 2023, Lawn et al. 2023) and orally administered THC and CBD-THC mixture were associated with anxiety (Zuardi et al. 1982). Some of the results suggested that CBD possibly modulated the psychological effects of inhaled THC as the mixture effects were significantly attenuated (Sainz-Cort et al. 2021) and potentiated (Lawn et al. 2023) compared to THC.

Lawn et al. (2023) high-quality study reported that both THC and 1:3 CBD-THC mixture were associated with psychotomimetic symptoms and increased PSI subscale scores. The cognitive disorganization subscale scores for the mixture were significantly higher than those for THC alone with a mean difference of 1.896, which was 48% of the 3.938 mean difference of THC relative to placebo. While the absolute difference was rather small, the relative difference was somewhat large and could suggest that CBD potentiated the cognitive disorganization associated with inhaled CBD-THC mixtures with a ratio of 3:1.

Studies of Morgan et al. (2018) and Englund et al. (2023) reported PSI results for mixtures with CBD:THC ratios of 2:1 and up to 3:1, respectively, and, compared to Lawn et al. (2023), at quite similar doses of THC at 8 mg and 10 mg, respectively. Nevertheless, they found no differences between THC and mixture effects. Englund et al. (2023) study was of very good quality with a large population, good methodology as well as excellent reporting. However, a poor-quality rating was warranted solely due to a critical flaw as the drop-out rate of the allocated study population exceeded 20% with many of the participants withdrawing due to adverse drug reactions. This could introduce a possibility of attrition bias as some cannabis effects, particularly the psychotic-like reactions are associated with individual vulnerability factors (Barkus and Lewis 2008, Mason et al. 2009) and withdrawal of the susceptible individuals from the study population could skew the results towards decreased psychological effects. For this reason, the absence of CBD modulatory effect on PSI results of Englund et al. (2023) does not necessarily contradict the positive result of Lawn et al. (2023).

Morgan et al. (2018) stratified their results by participant schizotypal traits and found that higher PSI scores in multiple subscales correlated with higher schizotypy, lending further support to the suggested interplay between individual susceptibility and psychotomimetic effects. They also reported similar PSI scores following mixture administration compared to THC alone. According to our best understanding the specifics about PSI scale and its questions have not been published, which complicates the interpretation of these results, particularly regarding whether the difference between treatments would have been noticeable to the participants of Lawn et al.

(2023) study. Despite the negative results in other studies, possibly clinically significant, albeit slight, potentiation of THC psychotomimetic effects by CBD in mixtures reported by Lawn et al. (2023) cannot be ruled out.

Sainz-Cort et al. (2021) reported that THC produced significant PSI score increases compared to placebo in in all the subscales except delusional thinking and anhedonia. CBD-THC mixture did not significantly increase the score of any subscale, but comparison to THC was statistically significant only for the cognitive disorganization subscale score. This could suggest that CBD attenuated the psychotomimetic effects of THC related to cognitive disorganization at high doses, even at rather low 2:1 ratio. However, as stated above, this study and especially the mixture interventions were likely affected by unreliable delivery of cannabinoids, so the reported differences between interventions were quite likely mostly due to different doses of delivered THC and not related to CBD modulation. Similarly, Zuardi et al. (1982), the only oral administration study reporting results for psychological outcomes, reported a smaller increase in anxiety following oral mixture administration compared to THC alone. However, this difference was not indicated as significant by statistical analysis contrasting these interventions and a high risk of misclassification bias discussed above further discourages confidence in any conclusions based on this result.

Evidence provided by the included studies does not support CBD modulation of the psychological effects of THC although there are some mixed results. A small amount of high-quality evidence suggests slight potentiation by CBD in inhaled mixtures at CBD:THC ratio of 3:1. Low-quality evidence also suggests that an attenuating modulatory effect could occur at a high inhaled CBD dose of 130 mg, even at low mixture ratio of 2:1. Because none of the oral studies reported statistically significant changes in psychological outcomes demonstrating differences between THC and mixture interventions, there is insufficient evidence to determine whether CBD modulates the psychological effects of orally ingested CBD-THC mixtures.

The influence of CBD on the acute effects of THC has been recently evaluated in a systematic review by Freeman et al. (2019). In their review, studies with CBD:THC mixture ratios of less than

two or mixed routes of administration for CBD and THC were not excluded. They concluded that CBD does not alter the subjective effects of THC but determined that psychological effects of anxiety and psychotomimetic symptoms were attenuated by CBD based primarily on studies where cannabinoids were administered through intravenous or mixed routes of administration. They also pointed out that individual vulnerability to psychotomimetic effects of THC may be a prerequisite to observing clinically significant CBD modulation of this outcome. Furthermore, mixed and inconsistent findings regarding CBD modulation of THC effects on memory precluded a solid conclusion regarding these aspects of cognition, but some evidence involving emotion and reward processing as well as psychomotor performance was deemed suggestive of CBD modulatory effects. Overall, the findings of this review were not markedly different from those presented in this thesis. A combination of inclusion of a larger number of studies with more heterogenous interventions compared to this thesis as well as the absence of the most recent well-conducted studies in their body of evidence likely contributed to the subtle differences in conclusions. It is also possible that pharmacokinetic nuances following mixed routes of administration are the key to producing clinically significant CBD modulatory effects, but they are not relevant to light cannabis or similar mixtures when both cannabinoids are administered via the same route.

## 6.3 Relevance of the results to evaluating hazard characteristics of light cannabis

Here, the relevance of these findings to light cannabis consumption is assessed. The intervention mixture ratios are compared to those characterized typical for composition of CBD-dominant light cannabis based on the sample data and the administered doses of THC are evaluated to determine whether they are in the range of those that could be expected to be associated with light cannabis consumption. Moreover, specific conditions associated with the interventions such as the simultaneity of cannabinoid administration and the duration of dose delivery need to be considered. Overlap between the sample- and intervention cannabinoid ratios (Figures 6A and 6B), relevance of the administered doses as well as suitability of the study conditions determine relevance of the intervention findings to evaluating hazard characteristics of light cannabis thus answering the second primary research question.

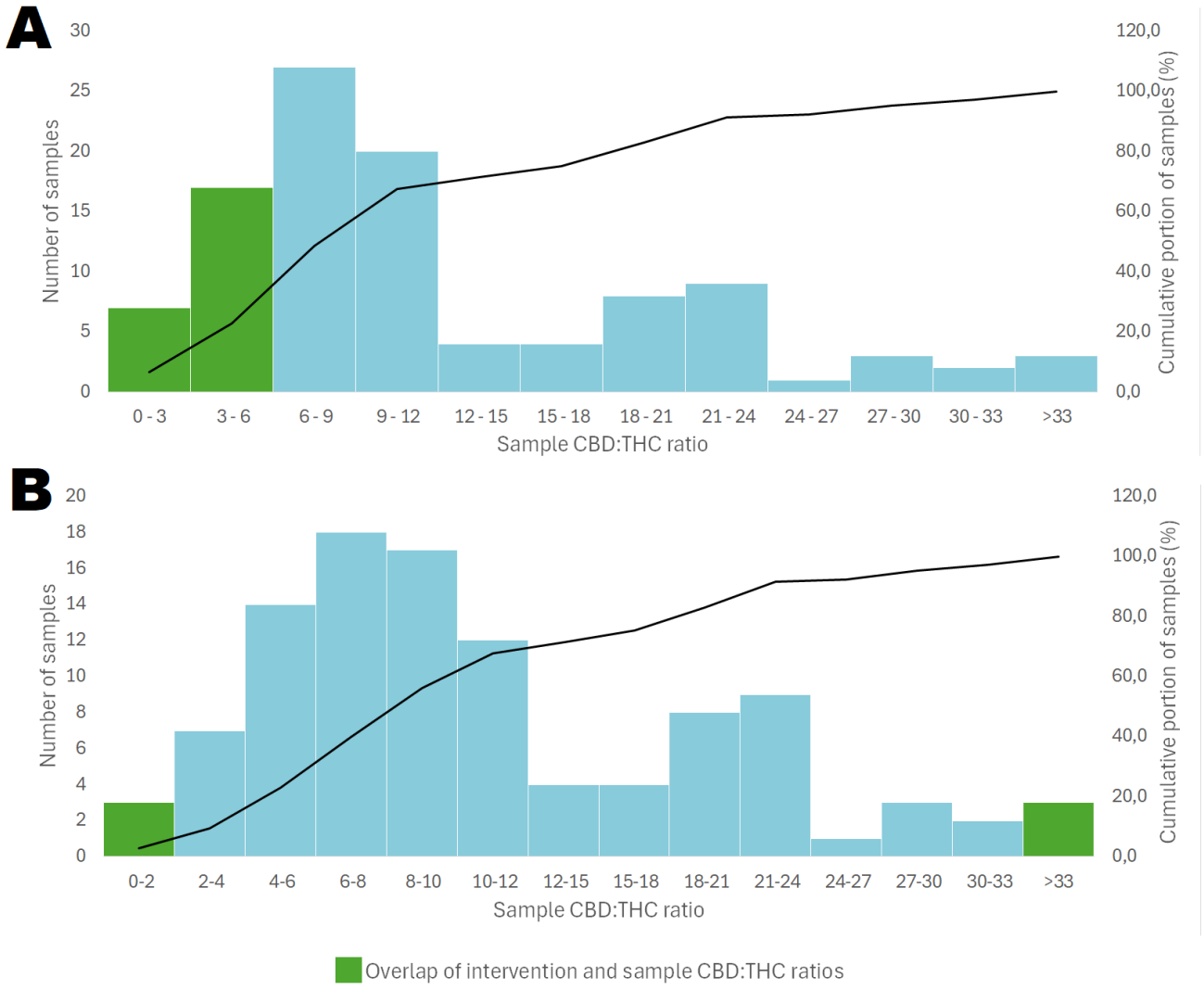


Figure 6. CBD:THC ratios of the analyzed light cannabis samples, cumulative portion of the samples according to ratio and the overlap of sample and intervention CBD:THC ratios for A inhalation studies and B oral studies.

### 6.3.1 Inhalation studies

CBD:THC ratios of the inhalation study interventions were between 2:1 and 6:1, corresponding to a cumulative 23% of the characterized samples and THC doses of 2-65 mg were administered. The inhalation intervention mixture ratios corresponded to a moderate degree to those typical for light cannabis, but largely due to a single study intervention with a ratio of 6:1. Otherwise, at

relevant ratios of 2:1 and 3:1 administered in the rest of the interventions, corresponding to a cumulative 6.7% of the characterized samples, intervention and sample mixture ratios had a very limited overlap (Figure 6A). The administered THC doses in range of 2-10 mg could reasonably be assumed to be rather typical for light cannabis consumption as doses ranging from 1.9 mg to 8.4 mg have been previously administered in clinical studies that attempted to replicate regular use scenarios of light cannabis smoking, as discussed in section 2.5.3.

Even though the participants of study by Pelletti et al. (2021) stated, after consuming three cigarettes equivalent to 4.92 mg of THC, that hardly more could be consumed in a recreational setting, the use of other paraphernalia for inhalation such as water pipes or vaporizers might allow for even larger doses of up to, or even exceeding, 10 mg in one session. Assuming average THC concentration of 2.5 mg/g based on the characterized samples, 10 mg of THC would correspond to about 4 grams of light cannabis. However, since joint smoking is the most prevalent method of cannabis consumption in Europe according to Hindocha et al. (2016), estimating consumption based on this assumption should account for the most typical scenarios of light cannabis use. Nevertheless, this is difficult to assess reliably in the absence of data about light cannabis consumption patterns. Additionally, the possible inhalation irritant properties of CBD, which are discussed in more detail below, might limit excessive dosing even when paraphernalia with higher throughput of cannabis were used. Therefore, the very high 65 mg THC dose administered in the study by Sainz-Cort et al. (2021) is unlikely to be relevant in the context of typical light cannabis consumption, but notably the 130 mg dose of CBD in the same study is the only one in the same range as the 100-232 mg CBD doses administered in the light cannabis studies discussed in section 2.5.3.

Simultaneous or near-simultaneous administration of study cannabinoids was critical for relevance of the inhalation interventions as this would ensure the best similarity of exposure with light cannabis consumption. All the studies included reported simultaneous administration, although Dalton et al. (1976) included an additional intervention with a 30-minute delay between CBD and THC inhalation with no modulatory effects reported. Another critical aspect that arises in the context of dosing cannabinoids via inhalation, is the time required to inhale a dose, as the

rapid absorption- and distribution kinetics of the inhalation route (Huestis 2005) may result in diminishing effects following prolonged delivery of a dose and resulting low dose rate. Interestingly, some of the studies included in this review reported difficulties in dose delivery related to irritating properties of the vaporized cannabinoids indicated by throat irritation, prolonged inhalation procedure completion time, and coughing. Englund et al. (2023) found a dose-responsive increase in inhalation time and coughing, and this longer inhalation time correlated with lower plasma peak cannabinoid and AUC concentrations. Similarly, Lawn et al. (2023) reported that it took significantly longer for the participants to inhale a mixture dose compared to a THC dose and this partially explained differences in the plasma THC levels between interventions.

Solowij et al. (2019) study was excluded from the systematic review, because difficulties in dose delivery resulted in THC doses being significantly different between the THC and mixture interventions at a CBD:THC ratio of 50:1. This dose-responsive, and apparently mixture ratio-related, increase in difficulty of dose inhalation might be due to the sheer amount of inhaled cannabinoids at larger doses and ratios, but it is also worth noting that CBD is a TRPV1 receptor full agonist, albeit a low potency one (Britch et al. 2021). It could be reasonably assumed that the irritating properties of vaporized cannabinoid mixtures could be partly due to CBD induced nociceptive sensory signaling caused by TRPV1 activation and the magnitude of this effect would correlate with CBD:THC ratio. This would suggest that while CBD does not appear to attenuate the effects of THC via pharmacological interaction, it could instead hinder the consumption of large doses of high ratio CBD:THC mixtures and thereby limit THC toxicity via irritating and possibly TRPV1 receptor associated effect in the context of light cannabis inhalation. However, the current studies are only suggestive of this effect as the relevant outcomes were generally not affected by increased inhalation times at the investigated mixture ratios (Englund et al. 2023, Lawn et al. 2023). Regardless, if CBD-related attenuation is not the reason for the unremarkable CNS effects observed in users of light cannabis, then low THC dose rates are likely the best explanation, as the estimated doses should be generally sufficient to produce intoxication.

Since most of the evidence did not support CBD modulation of the subjective effects of THC except for low-quality evidence suggesting slight attenuation, CBD is unlikely to modulate the subjective effects of inhaled light cannabis with up to 6:1 CBD:THC ratio. Similarly, Cognitive impairments related to information processing as well as psychological symptoms were not attenuated by CBD although evidence from a single high-quality study suggested a possible, albeit slight, potentiating effect of CBD on psychological effects of inhaled light cannabis with CBD:THC ratio of 3:1. However, Low-quality evidence suggested that CBD modulation attenuating the subjective and psychological effects could be associated with a high inhaled CBD dose of 130 mg, even at a low mixture ratio of 2:1, so the lack of observed modulatory effects may be due to lower doses of CBD in these interventions compared to those reasonably associated with light cannabis use. Despite this, the body of evidence does not support the conclusion that higher CBD content or CBD:THC ratio alone would mitigate the acute effects-related hazard characteristics of light cannabis consumed via inhalation when compared to those of drug-type cannabis.

### 6.3.2 Oral administration studies

Oral study interventions showed a large gap in the administered CBD:THC ratios. The lower studied ratios were at the threshold of relevant range at 2:1, only corresponding to a cumulative 2.9% of the characterized samples and one study had a very high mixture ratio of 40:1. THC doses of 20-40 mg were administered in these studies. Oral intervention cannabinoid ratios did not correspond well to those of the characterized samples, with intervention ratios being at the extreme ends of the range of ratios found in samples (Figure 6B). The typical patterns of oral consumption of light cannabis are very difficult if not impossible to estimate reliably in the absence of research data because the practical limitations are quite different compared to inhalation and much larger doses can be orally consumed. Nevertheless, the intervention THC doses appeared quite high as 8-16 grams of light cannabis with average characterized THC concentration of 2.5 mg/g would be required to reach the 20-40 mg doses.

A key aspect for relevance of oral interventions was simultaneous or near-simultaneous administration of the study cannabinoids for the best similarity of exposure to light cannabis

consumption. For most of the studies the administration was simultaneous, but in Woelfi et al. (2020) study there was a delay of 30 minutes. In this case, the short delay between CBD and THC was likely not sufficient to produce markedly different results compared to simultaneous administration. Nevertheless, this might have slightly exaggerated the possible modulatory effect of CBD due to earlier absorption and distribution presumably leading to comparably higher CBD concentrations in the CNS target tissues during the phase of THC distribution and binding to these tissues. This in turn would increase confidence in the negative results of this study. However, the modulatory effect of CBD might not have been observable as a change in the absolute effect magnitude but also as a delay in the change of outcome performance following THC administration. The study design did not allow for assessing this possible delay because of the non-simultaneous cannabinoid administration and limiting the assessment of subjective effects to only a single timepoint.

There was no credible evidence of CBD modulation of the subjective effects of THC at either end of the range of sample mixture ratios, which could tentatively suggest that CBD is inactive and does not modulate the THC subjective effects at any ratio. However, it could be possible that there is some nonlinear dose-effect relationship between oral CBD and THC with peak interaction occurring somewhere between the doses and ratios tested in the included studies. More evidence would be needed to confirm or refute this. Since Woelfi et al. (2020) was the only oral study to assess cognitive or psychological outcomes but the utilized THC dose was insufficient to produce robust impairment in either of these, it was not possible to make conclusions about the modulatory effects of CBD on these outcome categories for oral ingestion of light cannabis. The evidence was therefore insufficient to answer the secondary research question of whether the CBD modulatory effects are dependent on the route of administration. The body of evidence does not support the conclusion that higher CBD content or CBD:THC ratio alone would mitigate the acute effects-related hazard characteristics of light cannabis consumed via oral route compared to those of drug-type cannabis.

Previously it has been suggested that CBD may attenuate the adverse effects of THC (Englund et al. 2017) and a recommendation has been included into evidence-based lower-risk guidelines on

cannabis use to prefer the use of cannabis with high CBD:THC ratios due to CBD's attenuating effects on THC-related outcomes (Fischer et al. 2017). However, the findings presented in this thesis do not support a direct role for CBD or high CBD:THC ratio in lowering harms related to cannabis use. Nevertheless, as cannabis-related harm is associated with THC and the risks increase with higher THC concentrations (Curran et al. 2016) and a recommendation to prefer the use of low-potency THC cannabis is included in these same lower-risk guidelines by Fischer et al. (2017), the recommendation to choose CBD-dominant cannabis is still valid when understood as a proxy for choosing low-THC cannabis. Due to the interlinked biosynthesis of these cannabinoids (ElSholy et al. 2017), high CBD concentrations are generally indicative of low THC concentrations and thus decreased THC-related risk. Therefore, the choice of high CBD:THC ratio cannabis over low CBD:THC ratio cannabis is a valid risk reduction measure. While it is still possible that CBD itself may have some direct role at very high CBD:THC ratios, the current evidence is insufficient to elucidate this and further interventional studies with higher CBD-doses or ratios are required.

## 6.4 Sub-chronic and chronic exposures

Findings related to the secondary research question about whether there is evidence of CBD modulation of the sub-chronic or chronic effects of cannabinoid mixtures like those in light cannabis, are discussed here. The systematic search of literature only revealed acute intervention studies that enabled detection of possible CBD modulation of THC effects. One article by Kulpa et al. (2024) reporting repeated THC and mixture administration over 7 days of a 13-day study was initially considered but eventually not deemed eligible in the full-text review. This article combined results from two clinical trials (Peters 2022a, Peters 2022b) with similar doses of THC ranging from 5 to 20 mg administered via the oral route as products containing either nearly pure THC with a CBD:THC ratio of 0.012:1 or as a CBD-THC mixture with a ratio of about 22:1. However, since this article focused on bone turnover serum markers, no relevant outcomes were reported, and the article was therefore excluded. The results of the two separate reports on these individual trials were not directly comparable as per the inclusion and exclusion criteria but appeared to not suggest CBD modulation of THC effects. Similar subjective effects,

including levels of anxiety or paranoia, as well as similar levels of treatment emergent psychiatric disorders were reported for both treatments.

The included studies did not present much evidence supporting the possibility of clinically significant modulation of THC effects by CBD following acute exposure. However, many adverse effects of THC typically arise following repeated administration (Curran et al. 2016) and similarly it has been suggested that possible protective effects of CBD against THC harms require sub-chronic or chronic exposures to CBD. Two reports on the same study proposed that a 200 mg daily dose of oral CBD for 10 weeks in regular cannabis users improved cognitive function related to attention, learning and memory (SolowiJ et al. 2018) as well as restored hippocampal subfield volumes (Beale et al. 2018). Morgan et al. (2012) demonstrated sub-chronic cognitive improvements in individuals who use cannabis with CBD compared to users of cannabis devoid of it. Di Forti et al. (2015) study of first-episode psychosis patients reported a threefold increase in psychotic disorder in users of high-THC cannabis and a fivefold increase in daily users while the users of cannabis resin with lower THC and higher CBD concentrations did not differ from controls. These results suggest both individual as well as population level attenuation of mental health effects of cannabis associated with higher CBD:THC ratios and lower THC concentrations in cannabis products. Furthermore, the inclusion of CBD in Sativex® oromucosal medical cannabinoid spray has been justified by improvement of long-term safety of the product (Russo and Guy 2006, Boggs et al. 2016). Despite the lack of evidence of any remarkable acute interaction between THC and CBD, further investigation of the long-term benefits and risks of combining CBD with THC is still needed.

## 6.5 Considerations for future studies

Data gap in the interventional studies is evident regarding the CBD:THC mixture ratios relevant for light cannabis and studies investigating the relevant outcomes following inhalation as well as oral ingestion of 10:1, 20:1 and 30:1 mixtures are needed to close this gap. Furthermore, possible modulatory effects of inhaled CBD doses higher than 30 mg are not well elucidated and studies with higher ratios would address this problem as well. The need is especially dire for oral

studies investigating these high ratios and reporting cognitive and psychological outcomes for which the current research is insufficient. These studies should also utilize crossover designs and sufficiently large study populations as the currently available studies with oral interventions have been insufficient to account for the large interindividual variability of cannabinoid effects and have produced largely unreliable results (Button et al. 2013). Furthermore, oral studies should include investigation of possible delaying modulatory effect of CBD as well and include multiple measurement timepoints for the relevant outcomes.

Another vital consideration besides sufficiently large study populations and statistical power is consistent and reliable delivery of the intended cannabinoid doses to participants, as this seems to have been problematic in many of the past studies. While oral studies investigating high CBD:THC ratios should be relatively straightforward in terms of cannabinoid delivery, now that many well-characterized pharmaceutical formulations are available for use in clinical studies, inhalation studies of mixtures with high ratios may be somewhat more complicated. Inhalation studies even at relatively low ratios have encountered difficulties related to dose delivery (Englund et al. 2023, Lawn et al. 2023), presumably due to irritating properties of the cannabinoid vapors and particularly CBD, when large doses are inhaled. The doses of THC delivered as a part of these inhaled mixtures need to be sufficient to induce robust effects in the relevant outcomes and since it appears that at least 8-10 mg of THC is required (Kleinloog et al. 2014), the total dose of cannabinoids could exceed 300 mg for a study with 30:1 mixture intervention. Protocol validation to ensure the reliability of dose delivery and practical design to facilitate consistency of the inhalation procedure are key considerations for successful execution of these studies.

Lastly, well-controlled studies investigating the role of CBD in sub-chronic or chronic effects of cannabinoid mixtures are necessary. Not only for understanding the human health effects of light cannabis but also to potentially improve the safety of medical cannabis products and their use. Even though the current findings are generally not suggestive of CBD modulatory effect in acute outcomes and do not necessarily encourage such studies, the low health risks associated

with these types of studies, when they are expertly conducted, do not warrant for their omission either.

## 6.6 Limitations

The aim of this study was to understand the effects of light cannabis in humans, and it was specifically defined in this work as a low-THC cannabis product with full spectrum of cannabinoids. However, many of the included intervention studies used pure THC and CBD alone, which allowed for isolating the effects and interplay between these two cannabinoids, but poorly captured the chemical and pharmacological diversity of the full spectrum of plant components. Similarly, the characterization of light cannabis composition in this thesis was based only on THC, CBD and CBN and thus considered a rather narrow cross-section of the complete chemistry, as was also the case for those intervention studies that utilized full spectrum-cannabis but focused solely on THC and CBD when analyzing and presenting their findings. Nevertheless, findings were similar for interventions with purified CBD and THC as well as for those with full spectrum-cannabis. Constraining the scope of work to a limited number of cannabinoids may be often necessary for practical reasons but is an inherent limitation as well.

Most of the studies included in the qualitative synthesis were evaluated as poor or fair in terms of study quality due to limitations in methodology and reporting of study details. They often involved ambiguous randomization or allocation of the participants and had small study or group sizes. Many of the included studies utilized THC doses that corresponded adequately to those that might reasonably be associated with light cannabis consumption. However, cannabinoid mixture ratios of the interventions did not correspond well to those identified as typical when characterizing the composition of light cannabis but instead only represented the lower and the very high end of the sample variation. Critically, almost all the intervention doses of inhaled CBD were much lower than those reasonably associated with light cannabis consumption. As a result, findings of the included studies were applicable to only a small fraction of the mixture ratios observed in light cannabis samples.

It is also worth noting that the characterization of light cannabis in this thesis was based on a relatively low number of samples and as such the determined characteristics may not be representative of the entire variability or trends in the composition of CBD-dominant light cannabis. Furthermore, as there was no real-life data available on the typical consumption patterns of light cannabis, it was difficult to estimate how well the findings corresponded to THC doses typically consumed in the context of light cannabis use. Therefore, rough assumptions based on the few available clinical light cannabis studies as well as those investigating patterns of regular cannabis use, were necessary, and as such only limited confidence can be placed on the accuracy of these estimates.

There is a plethora of difficulties related to various confounding factors, which would have been particularly challenging for a study investigating the role of CBD in high CBD:THC ratio mixture effects and based on cross-sectional or epidemiological data. Therefore, it was necessary to rely on clinical trials. Only acute, single exposure studies were included in the systematic review as none of the screened repeated exposure studies were deemed suitable for answering the research questions. As a result, the scope of findings in this thesis only allows for generalizing about the acute effects of CBD-THC mixtures while many of the adverse effects of cannabis are primarily associated with repeated or long-term use. Associations or correlations of the acute effects of cannabis with the long-term effects are currently not well understood and thus, sub-chronic or chronic studies are required to elucidate the health consequences of repeated use of light cannabis and similar CBD-THC mixtures.

Lastly, the systematic review of literature was performed by a single individual, which could introduce a risk of bias. However, none of the included and excluded articles were ambiguous regarding the selection criteria or their results and therefore it is unlikely that duplication of the screening or data extraction steps by another individual would have produced different results, so impact of this limitation is likely small. Nevertheless, the quality assessment involved somewhat considerable subjective interpretation of the study reporting, so omitting the duplication of this process likely introduced some risk of bias.

## 6.7 Conclusions

The articles included in this systematic review did not demonstrate appreciable modulation of THC induced acute subjective effects, cognitive impairment, or psychological symptoms by CBD at the mixture doses and ratios of THC and CBD administered to the participants. This was true for both inhalation and oral administration of study cannabinoids. Where an analysis of the study quality, details of the study and interventions, as well as the consistency of results between the studies suggested a modulatory effect to likely be a true effect and attributable to CBD, its magnitude was so small that it was questionable whether it would have been perceptible to the participants and thus truly clinically significant. Evidence was insufficient to determine whether this possible modulatory effect was affected by the route of administration.

The findings of the interventional studies included in the systematic review were only partially suitable for establishing conclusions about the effects of light cannabis in humans. The ratios of CBD and THC utilized in the interventions had poor overlap with those found in the mixtures present in light cannabis samples. For inhalation studies, the intervention CBD:THC ratios represented a quarter of the samples at the low end of sample ratios while the oral study intervention ratios represented about a tenth of the samples with ratios at low and high ends of the measured range. THC doses in inhalation studies were mostly in the range that could be reasonably assumed typical for light cannabis consumption, whereas for oral study interventions the THC doses were higher. Both inhalation and oral study interventions had mostly lower doses of CBD than likely typical for light cannabis consumption. Thereby the intervention mixture compositions and doses only partially corresponded to the assumptions of typical light cannabis consumption. However, both inhalation and oral interventions involved simultaneous or sufficiently nearly simultaneous administration of the mixture cannabinoids to adequately represent that of light cannabis either via inhalation or oral route of administration.

In summary, this thesis only allows for conclusions that are limited to the overlapping range of intervention and sample mixture ratios as well as the administered doses of cannabinoids. While the ranges explored were not suggestive of CBD modulation of THC acute effects, it is still possible that higher CBD doses and mixture ratios could be demonstrated to produce clinically

significant modulatory effects. However, as of now there are no findings in literature that would be more than tentatively suggestive of this possibility at higher CBD doses or ratios for acute effects, and there are no relevant findings related to sub-chronic or chronic effects that would allow determining the role of CBD in pharmacology of cannabinoid mixtures with high CBD:THC ratios. In conclusion, CBD modulation of THC-related outcomes appears to have a negligible effect on the hazard characteristics of light cannabis. The current evidence does not warrant treating CBD-dominant light cannabis differently from drug-type cannabis in risk assessments solely due to higher CBD concentrations or CBD:THC ratios and based on assumptions about attenuating effects of CBD on THC-related hazards. Therefore, these assessments should primarily focus on the differences in THC concentrations unless future work in the field produces more conclusive evidence supporting CBD modulation of light cannabis effects.

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# Appendices

## Appendix A

Cannabinoid concentrations measured by Marchei et al. (2020) CBD:THC ratios and total cannabinoid fractions (Cf%) derived from reported results (Bolded). Samples in this study were analyzed with both HPLC/MS-MS and GC-MS, but only the GC-MS results are shown here and were selected for the higher reported THC concentrations.

| Sample | THC% (GC-MS) mean | THC% (GC-MS) SD* | CBD% (GC-MS) mean | CBD% (GC-MS) SD | Cf% mean | CBD:THC mean |
|---|---|---|---|---|---|---|
| 1 | **0.1** | **0.04** | **2.2** | **0.12** | 2.30 | 22.0 |
| 2 | **0.1** | **0.03** | **2.75** | **0.15** | 2.85 | 27.5 |
| 3 | **0.16** | **0.04** | **3.1** | **0.2** | 3.26 | 19.4 |
| 4 | **0.17** | **0.04** | **3.2** | **0.1** | 3.37 | 18.8 |
| 5 | **0.25** | **0.06** | **4.75** | **0.14** | 5.00 | 19.0 |
| 6 | **0.23** | **0.03** | **5.05** | **0.12** | 5.28 | 22.0 |
| 7 | **0,16** | **0.04** | **4.5** | **0.12** | 4.66 | 28.1 |
| 8 | **0.32** | **0.08** | **2.2** | **0.07** | 2.52 | 6.9 |
| 9 | **0.28** | **0.04** | **6.2** | **0.05** | 6.48 | 22.1 |
| 10 | **0.39** | **0.05** | **8.2** | **0.12** | 8.59 | 21.0 |
| 11 | **0.28** | **0.04** | **5.8** | **0.15** | 6.08 | 20.7 |
| 12 | **0.19** | **0.04** | **4.3** | **0.14** | 4.49 | 22.6 |
| Mean | 0.22 | | 4.35 | | 4.57 | 20.8 |
| Median | 0.21 | | 4.40 | | 4.58 | 21.5 |
| SD | 0.09 | | 1.80 | | 1.86 | 5.3 |

*Standard deviations of samples done in triplicate

Cannabinoid concentrations measured by Fabresse et al. (2022) CBD:THC ratios and total cannabinoid fractions (Cf%) derived from reported results (Bolded)

| Sample | THC% | CBD% | CBN% | Cf% | THC:CBD | CBD:THC* |
|---|---|---|---|---|---|---|
| 1 | **0.26** | **1.6** | **0.014** | 1.87 | **0.16** | 6.3 |
| 2 | **0.32** | **2.4** | **0.007** | 2.73 | **0.13** | 7.7 |
| 3 | **0.3** | **2.9** | **0.007** | 3.21 | **0.1** | 10.0 |
| 4 | **0.22** | **2.1** | **0.01** | 2.33 | **0.1** | 10.0 |
| 5 | **0.2** | **1.8** | **0,009** | 2.01 | **0.12** | 8.3 |
| 6 | **0.25** | **2.1** | **0.008** | 2.36 | **0.12** | 8.3 |
| 7 | **0.07** | **0.9** | **0.06** | 1.03 | **0.08** | 12.5 |
| 8 | **0.03** | **0.3** | **0** | 0.33 | **0.13** | 7.7 |
| 9 | **0.1** | **0.9** | **0** | 1.00 | **0.11** | 9.1 |
| 10 | **0.07** | **0.01** | **0** | 0.08 | **8.74** | 0.1 |
| 11 | **0.15** | **1.1** | **0** | 1.25 | **0.14** | 7.1 |
| 12 | **0.46** | **3.4** | **0** | 3.86 | **0.14** | 7.1 |
| 13 | **0.22** | **1.3** | **0** | 1.52 | **0.17** | 5.9 |
| 14 | **0.18** | **0.9** | **0** | 1.08 | **0.2** | 5.0 |
| 15 | **0.05** | **0.2** | **0** | 0.25 | **0.32** | 3.1 |
| 16 | **0.5** | **3.2** | **0** | 3.70 | **0.16** | 6.3 |
| 17 | **0.04** | **0.51** | **0** | 0.55 | **0.08** | 12.5 |
| 18 | **0.77** | **5.64** | **0.007** | 6.42 | **0.14** | 7.1 |
| 19 | **0.68** | **5.97** | **0.007** | 6.66 | **0.11** | 9.1 |
| 20 | **0.2** | **2.35** | **0** | 2.55 | **0.08** | 12.5 |
| 21 | **0.1** | **1.16** | **0** | 1.26 | **0.08** | 12.5 |
| 22 | **0.61** | **0.16** | **0.007** | 0.78 | **3.7** | 0.3 |

| Sample | THC% | CBD% | CBN% | Cf% | THC:CBD | CBD:THC* |
|---|---|---|---|---|---|---|
| 23 | **0.1** | **1.08** | **0** | 1.18 | **0.09** | 11.1 |
| 24 | **0.48** | **5.72** | **0.021** | 6.22 | **0.08** | 12.5 |
| 25 | **0.46** | **3.28** | **0.007** | 3.75 | **0.14** | 7.1 |
| 26 | **0.27** | **1.48** | **0** | 1.75 | **0.18** | 5.6 |
| 27 | **0.52** | **4.99** | **0.021** | 5.53 | **0.11** | 9.1 |
| 28 | **0.3** | **1.98** | **0.005** | 2.29 | **0.15** | 6.7 |
| 29 | **0.57** | **5.02** | **0.025** | 5.62 | **0.11** | 9.1 |
| 30 | **0.7** | **1.48** | **0.005** | 2.19 | **0.47** | 2.1 |
| 31 | **0.32** | **1.85** | **0** | 2.17 | **0.17** | 5.9 |
| 32 | **0.2** | **0.93** | **0** | 1.13 | **0.21** | 4.8 |
| 33 | **0.5** | **3.75** | **0.018** | 4.27 | **0.13** | 7.7 |
| 34 | **0.38** | **1.79** | **0.004** | 2.17 | **0.21** | 4.8 |
| 35 | **0.24** | **1.05** | **0** | 1.29 | **0.23** | 4.3 |
| 36 | **0.61** | **4.31** | **0** | 4.92 | **0.14** | 7.1 |
| 37 | **0.2** | **1.68** | **0** | 1.88 | **0.12** | 8.3 |
| 38 | **0.37** | **2.6** | **0** | 2.97 | **0.14** | 7.1 |
| 39 | **0.38** | **3.23** | **0.008** | 3.62 | **0.12** | 8.3 |
| **Mean** | **0.32** | **2.23** | **0.01** | 2.56 | **0.5** | 7.4 |
| **Median** | 0.27 | 1.8 | 0 | 2.17 | 0.14 | 7.1 |
| **Sd** | 0.20 | 1.62 | 0.01 | 1.78 | 1.48 | 3.1 |

*CBD:THC ratios determined from THC:CBD ratios with equation (2)

Cannabinoid concentrations measured by Amendola et al. (2021) CBD:THC ratios and total cannabinoid fractions derived from reported results (Bolded)

| Sample* | THC% | CBD% | Cf% | CBD:THC |
|---|---|---|---|---|
| 1 | **0.05** | **0.36** | 0.41 | 7.2 |
| 2 | **0.15** | **0.68** | 0.83 | 4.5 |
| 3 | **0.21** | **1.43** | 1.64 | 6.8 |
| 4 | **0.38** | **4.14** | 4.52 | 10.9 |
| 5 | **0.46** | **0.92** | 1.38 | 2.0 |
| 6 | **0.09** | **0.48** | 0.57 | 5.3 |
| 7 | **0.48** | **3.17** | 3.65 | 6.6 |
| 8 | **0.39** | **8.64** | 9.03 | 22.2 |
| 9 | **0.22** | **0.82** | 1.04 | 3.7 |
| 10 | **0.13** | **1.5** | 1.63 | 11.5 |
| 11 | **0.18** | **1.95** | 2.13 | 10.8 |
| 12 | **0.26** | **2.67** | 2.93 | 10.3 |
| 13 | **0.25** | **2.97** | 3.22 | 11.9 |
| 14 | **0.19** | **2.1** | 2.29 | 11.1 |
| 15 | **0.07** | **0.66** | 0.73 | 9.4 |
| 16 | **0.08** | **1.17** | 1.25 | 14.6 |
| 17 | **0.1** | **1.88** | 1.98 | 18.8 |
| 18 | **0.05** | **1.18** | 1.23 | 23.6 |
| 19 | **0.06** | **0.4** | 0.46 | 6.7 |
| 20 | **0.07** | **0.58** | 0.65 | 8.3 |
| 21 | **0.1** | **1.2** | 1.30 | 12.0 |
| 22 | **0.44** | **3.48** | 3.92 | 7.9 |

| Sample* | THC% | CBD% | Cf% | CBD:THC |
|---|---|---|---|---|
| 23 | **0.06** | **0.3** | 0.36 | 5.0 |
| 24 | **0.08** | **0.81** | 0.89 | 10.1 |
| 25 | **0.08** | **0.67** | 0.75 | 8.4 |
| 26 | **0.13** | **0.55** | 0.68 | 4.2 |
| 27 | **0.17** | **0.83** | 1.00 | 4.9 |
| 28 | **0.15** | **0.43** | 0.58 | 2.9 |
| 29 | **0.26** | **0.79** | 1.05 | 3.0 |
| 30 | **0.13** | **0.55** | 0.68 | 4.2 |
| Mean | **0.18** | **1.58** | 1.76 | 9.0 |
| Median | **0.14** | **0.88** | 1.14 | 8.1 |
| Sd | 0.13 | 1.68 | 1.77 | 5.4 |

*One sample with no reported cannabinoid concentrations omitted from the table

Cannabinoid concentrations measured by Nava et al. (2022). CBD:THC ratios and total cannabinoid fractions derived from reported results (Bolded)

| Sample | THC% mean | THC% SD* | CBD% mean | CBD% SD* | CBN% mean | CBN% SD* | Cf% mean | CBD:THC mean |
|---|---|---|---|---|---|---|---|---|
| 1 | **0.28** | **0.03** | **5.55** | **0.99** | **0.07** | **0** | 5.9 | 19.8 |
| 2 | **0.42** | **0.05** | **1.05** | **0.05** | **0.14** | **0.03** | 1.61 | 2.5 |
| 3 | **0.25** | **0.04** | **5.47** | **0.05** | **0.12** | **0.01** | 5.84 | 21.9 |
| 4 | **0.18** | **0.05** | **2.92** | **0.06** | **0.03** | **0.01** | 3.13 | 16.2 |
| 5 | **0.19** | **0.04** | **4.86** | **0.1** | **0.08** | **0.02** | 5.13 | 25.6 |
| 6 | **0.37** | **0.12** | **1.24** | **0.08** | **0.22** | **0** | 1.83 | 3.4 |
| 7 | **0.25** | **0.06** | **7.62** | **0.09** | **0.26** | **0.01** | 8.13 | 30.5 |
| 8 | **0.27** | **0.04** | **2.35** | **0.49** | **0.2** | **0.02** | 2.82 | 8.7 |

| Sample | THC% mean | THC% SD* | CBD% mean | CBD% SD* | CBN% mean | CBN% SD* | Cf% mean | CBD:THC mean |
|---|---|---|---|---|---|---|---|---|
| 9 | **0.33** | **0.03** | **7.65** | **0.09** | **0.12** | **0.05** | 8.1 | 23.2 |
| 10 | **0.33** | **0.06** | **2.12** | **0.12** | **0.11** | **0.01** | 2.56 | 6.4 |
| 11 | **0.11** | **0.05** | **6.35** | **0.62** | **0.16** | **0.01** | 6.62 | 57.7 |
| 12 | **0.3** | **0.05** | **1.72** | **0.06** | **0.24** | **0.05** | 2.26 | 5.7 |
| 13 | **0.37** | **0.06** | **7.76** | **0.09** | **0.11** | **0** | 8.24 | 21.0 |
| 14 | **0.36** | **0.06** | **3.26** | **1.21** | **0.2** | **0.06** | 3.82 | 9.1 |
| 15 | **0.39** | **0.06** | **6.03** | **0.94** | **0.3** | **0.05** | 6.72 | 15.5 |
| 16 | **0.1** | **0.05** | **3.03** | **0.11** | **0.2** | **0.06** | 3.33 | 30.3 |
| 17 | **0.34** | **0.06** | **7.76** | **0.13** | **0.07** | **0** | 8.17 | 22.8 |
| 18 | **0.22** | **0.03** | **1.9** | **0.06** | **0.26** | **0.08** | 2.38 | 8.6 |
| 19 | **0.13** | **0.04** | **8.78** | **2.03** | **0.05** | **0.01** | 8.96 | 67.5 |
| 20 | **0.13** | **0.04** | **1.74** | **0.06** | **0.07** | **0** | 1.94 | 13.4 |
| 21 | **0.08** | **0.03** | **5.3** | **1.06** | **0.04** | **0** | 5.42 | 66.3 |
| 22 | **0.15** | **0.03** | **2.52** | **0.19** | **0.27** | **0.07** | 2.94 | 16.8 |
| 23 | **0.2** | **0.07** | **5.45** | **0.97** | **0.14** | **0.01** | 5.79 | 27.3 |
| 24 | **0.15** | **0.05** | **2.57** | **0.07** | **0.07** | **0** | 2.79 | 17.1 |
| Mean | **0.4** | | **4.39** | | **0.14** | | 4.77 | 22.4 |
| Median | **0.25** | | **4.06** | | **0.13** | | 4.48 | 18.5 |
| Sd | 0.1 | | 2.44 | | 0.08 | | 2.42 | 18.0 |

*Standard deviations of samples done in triplicate

**Appendix B**

Search terms used in PubMed Advanced search.

| |
|---|
| #1 "light cannabis" OR "cannabis light" OR "industrial cannabis" OR "industrial hemp" OR "medical cannabis" OR "medical mari*" OR "medicinal cannabis" OR "medicinal mari*" OR "low tetrahydrocannabinol" OR low-tetrahydrocannabinol OR "low THC" OR low-THC OR low-delta-9-THC OR "low delta-9-THC" OR low-delta-9-tetrahydrocannabinol OR "low delta-9-tetrahydrocannabinol" OR bedrolite OR "CBD THC" OR "THC CBD" |
| #2 "cannabidiol dominant" OR cannabidiol-dominant OR "CBD dominant" OR CBD-dominant OR "cannabidiol enriched" OR cannabidiol-enriched OR "CBD enriched" OR CBD-enriched OR "high cannabidiol" OR high-cannabidiol OR "high CBD" OR high-CBD OR "cannabidiol rich" OR cannabidiol-rich OR "CBD rich" OR CBD-rich OR CBDistillery OR CBDodgamax |
| #3 #1 OR #2 |
| #4 interacti* OR synerg* OR potentiat* OR attenuat* OR interference* OR modulat* OR ameliorat* OR subjective OR mediat* OR moderat* |
| #5 "endocannabinoid system*" OR intoxicat* OR pharmacodynamic* OR "dose response" OR "perceptual distort*" OR euphori* OR "visual analogue scale" OR "visual analog scale" OR VAS OR relax* OR sedat* OR depress* OR dysphori* OR "time perception" OR "feeling high" OR "high feeling*" OR stoned OR "drug effect*" OR elation OR subjective |
| #6 cogniti* OR memory OR attention* OR recall OR learning OR affect* OR emotion* OR performance OR behavio* OR psychomotor OR psychological* OR neuropsycholog* OR neurophysiolog* OR psychiatr* OR hippocamp* OR "facial recognition" OR "mental recall" |
| #7 anxiet* OR anxiogenic* OR anxious OR psychos* OR psychot* OR schizo* OR paranoi* OR delusion* OR dissociat* OR perception OR perceptual |
| #8 #4 OR #5 OR #6 OR #7 |
| #9 #3 AND #8 |
| #10 #9 NOT (review OR "meta analysis" OR editorial OR letter OR conference OR proceedings) |
| #11 #10 AND (human OR humans) |
| #12 #11 AND (adult OR adults OR "middle age" OR aged OR aging OR elder* OR "old person*" OR "old people" OR senior* OR "older person*" OR "older people") |
| #13 #12 AND english[la] |

**Appendix C**

Full list of criteria included in the NHLBI study quality assessment tool of controlled intervention studies. NHLBI 2021 - https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools

Quality Assessment of Controlled Intervention Studies

| Criteria | Yes | No | Other (CD, NR, NA)* |
|---|---|---|---|
| 1. Was the study described as randomized, a randomized trial, a randomized clinical trial, or an RCT? | | | |
| 2. Was the method of randomization adequate (i.e., use of randomly generated assignment)? | | | |
| 3. Was the treatment allocation concealed (so that assignments could not be predicted)? | | | |
| 4. Were study participants and providers blinded to treatment group assignment? | | | |
| 5. Were the people assessing the outcomes blinded to the participants' group assignments? | | | |
| 6. Were the groups similar at baseline on important characteristics that could affect outcomes (e.g., demographics, risk factors, co-morbid conditions)? | | | |
| 7. Was the overall drop-out rate from the study at endpoint 20% or lower of the number allocated to treatment? | | | |
| 8. Was the differential drop-out rate (between treatment groups) at endpoint 15 percentage points or lower? | | | |
| 9. Was there high adherence to the intervention protocols for each treatment group? | | | |
| 10. Were other interventions avoided or similar in the groups (e.g., similar background treatments)? | | | |
| 11. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants? | | | |
| 12. Did the authors report that the sample size was sufficiently large to be able to detect a difference in the main outcome between groups with at least 80% power? | | | |
| 13. Were outcomes reported or subgroups analyzed prespecified (i.e., identified before analyses were conducted)? | | | |
| 14. Were all randomized participants analyzed in the group to which they were originally assigned, i.e., did they use an intention-to-treat analysis? | | | |

**Quality Rating (Good, Fair, or Poor)**

Rater #1 initials:

Rater #2 initials:

Additional Comments (If POOR, please state why):

*CD, cannot determine; NA, not applicable; NR, not reported

**Appendix D**

List of excluded full-text screened studies with reason for exclusion.

| Reference | Study name | Reason for exclusion after full-text screening |
|---|---|---|
| Aviram et al. 2021 | Specific phytocannabinoid compositions are associated with analgesic response and adverse effects in chronic pain patients treated with medical cannabis. | Exclusion principle - doses of administered CBD or THC not specified for individual participants |
| Bhattacharyya et al. 2010 | Opposite effects of delta-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. | Exclusion principle - route of administration for CBD and THC not inhalation or oral |
| Bhattacharyya et al. 2012 | Induction of psychosis by Δ9-tetrahydrocannabinol reflects modulation of prefrontal and striatal function during attentional salience processing. | No simultaneous administration of THC and CBD |
| Bhattacharyya et al. 2015 | Cannabinoid modulation of functional connectivity within regions processing attentional salience. | No simultaneous administration of THC and CBD |
| Brunt et al. 2014 | Therapeutic satisfaction and subjective effects of different strains of pharmaceutical-grade cannabis. | Too low CBD:THC ratio (Highest CBD 7,5%/THC 6% = 1.25) |
| Eichler et al. 2012 | Heat exposure of Cannabis sativa extracts affects the pharmacokinetic and metabolic profile in healthy male subjects. | Too low CBD:THC ratio (Highest CBD 28.6 mg/ THC 19.8 mg = 1.44) |
| Hindocha et al. 2020 | Acute effects of cannabinoids on addiction endophenotypes are moderated by genes encoding the CB1 receptor and FAAH enzyme. | Not all participants are older than 18 years old (age range 16-23) and there is no separately analyzed adults-only subgroup |
| Johnson et al. 2010 | Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC:CBD extract and THC extract in patients with intractable cancer-related pain. | Too low CBD:THC ratio (sativex 1:1) |

| Reference | Study name | Reason for exclusion after full-text screening |
|---|---|---|
| Kayser et al. 2020 | Acute effects of cannabinoids on symptoms of obsessive-compulsive disorder: A human laboratory study. | Exclusion principle -THC dose not same or equivalent in THC-only and CBD-dominant cannabis administrations |
| Kulpa et al. 2024 | Serum Markers of Bone Turnover Following Controlled Administration of Two Medical Cannabis Products in Healthy Adults. | Exclusion principle - no relevant outcomes reported |
| Morgan et al. 2010 | Impact of cannabidiol on the acute memory and psychotomimetic effects of smoked cannabis: naturalistic study: naturalistic study [corrected]. | Too low CBD:THC ratio |
| Pellesi et al. 2018 | Pharmacokinetics and tolerability of oral cannabis preparations in patients with medication overuse headache (MOH)-a pilot study. | Exclusion principle - no THC-only administration |
| Skumlien et al. 2023 | The Effects of Acute Cannabis With and Without Cannabidiol on Neural Reward Anticipation in Adults and Adolescents. | Exclusion principle - no relevant outcomes reported |
| Solowij et al. 2019 | A randomised controlled trial of vaporised Δ(9)-tetrahydrocannabinol and cannabidiol alone and in combination in frequent and infrequent cannabis users: acute intoxication effects. | Exclusion principle - THC dose not same or equivalent for THC-only treatment and CBD+THC treatment |
| van de Donk et al. 2019 | An experimental randomized study on the analgesic effects of pharmaceutical-grade cannabis in chronic pain patients with fibromyalgia. | Exclusion principle -THC dose not same or equivalent in THC-only and CBD-dominant cannabis administrations |

**Appendix E**

Available relevant data of study by Karniol et al. (1974).

| Assessment or measurement | Placebo | CBD | CBD | CBD | THC | CBD + THC | CBD + THC | CBD + THC |
|---|---|---|---|---|---|---|---|---|
| Dose of CBD and THC | - | 15 mg | 30 mg | 60 mg | 30 mg | 30 mg + 15 mg | 30 mg + 30 mg | 30 mg + 60 mg |
| CBD:THC ratio | - | 1:0 | 1:0 | 1:0 | 0:1 | 1:2 | 1:1 | 2:1 |
| Psychological reaction group median | 0 | 0 | 0 | 0 | 4 | 2 | 1 | 2 |
| Psychological reaction grade 0 (number of subjects) | 5 | 4 | 4 | 5 | 0 | 0 | 0 | 0 |
| Psychological reaction grade 1 (number of subjects) | 0 | 1 | 1 | 0 | 0 | 0 | 3 | 2 |
| Psychological reaction grade 2 (number of subjects) | 0 | 0 | 0 | 0 | 1 | 3 | 1 | 3 |
| Psychological reaction grade 3 (number of subjects) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Psychological reaction grade 4 (number of subjects) | 0 | 0 | 0 | 0 | 4 | 2 | 1 | 2 |
| Time production without feedback T1 (baseline) – mean (SE) | 58.3 (3.1) | 58.3 (3.1) | 58.3 (3.1) | 58.3 (3.1) | 58.3 (3.1) | 58.3 (3.1) | 58.3 (3.1) | 58.3 (3.1) |
| Time production with feedback T2 (baseline) – mean (SE) | 59.8 (2.1) | 59.8 (2.1) | 59.8 (2.1) | 59.8 (2.1) | 59.8 (2.1) | 59.8 (2.1) | 59.8 (2.1) | 59.8 (2.1) |
| Time production without feedback T3 (45 min) – mean (SE) | 58.3 (1.0) | 49.0 (1.8) | 60.0 (1.5) | 57.1 (1.2) | 33.6 (2.1) | 49.2 (3.0) | 51.8 (2.1) | 50.0 (1.4) |
| Time production with feedback T4 (45 min) – mean (SE) | 59.6 (0.6) | 61.7 (1.4) | 60.5 (1.0) | 59.8 (1.0) | 40.2 (2.6) | 57.9 (1.9) | 56.6 (2.0) | 58.4 (1.7) |
| Time production without feedback T5 (95 min) – mean (SE) | 59.4 (0.7) | 54.0 (1.1) | 55.8 (1.8) | 56.8 (0.8) | 39.6 (2.1) | 54.4 (2.7) | 50.9 (1.5) | 54.7 (1.5) |

| Assessment or measurement | Placebo | CBD | CBD | CBD | THC | CBD + THC | CBD + THC | CBD + THC |
|---|---|---|---|---|---|---|---|---|
| Time production with feedback T6 (95 min) – mean (SE) | 59.6 (0.7) | 62.0 (1.1) | 59.4 (0.8) | 60.9 (0.7) | 49.2 (3.3) | 62.7 (2.5) | 55.8 (1.8) | 59.9 (2.2) |
| Time production without feedback T7 (180 min) – mean (SE) | 57.8 (1.4) | 55.1 (1.5) | 58.4 (2.1) | 62.4 (1.0) | 39.3 (2.5) | 55.7 (2.3 | 45.8 (1.7) | 56.9 (2.4) |
| Time production with feedback T8 (180 min) – mean (SE) | 59.9 (0.6) | 62.4 (1.3) | 60.5 (1.3) | 60.6 (0.6) | 51.0 (2.7) | 63.2 (2.3) | 56.7 (2.3) | 57.9 (1.2) |

Available relevant p-values for study by Karniol et al. (1974).

| Assessment or measurement | CBD vs. placebo | THC vs. placebo | CBD+THC (2:1) vs. placebo* | CBD+THC (2:1) vs. THC* |
|---|---|---|---|---|
| Psychological reaction group median | NR | p≤0.05 | p≤0.05 | p≤0.05 |
| Psychological reaction grade 0 | - | - | - | - |
| Psychological reaction grade 1 | - | - | - | - |
| Psychological reaction grade 2 | - | - | - | - |
| Psychological reaction grade 3 | - | - | - | - |
| Psychological reaction grade 4 | - | - | - | - |
| Time production without feedback T1 (baseline) | ns. | ns. | ns. | ns. |
| Time production with feedback T2 (baseline) | ns. | ns. | ns. | ns. |
| Time production without feedback T3 (45 min) | p≤0.05 | p≤0.05 | p≤0.05 | p≤0.05 |
| Time production with feedback T4 (45 min) | ns. | p≤0.05 | ns. | p≤0.05 |
| Time production without feedback T5 (95 min) | p≤0.05 | p≤0.05 | p≤0.05 | p≤0.05 |
| Time production with feedback T6 (95 min) | ns. | p≤0.05 | ns. | p≤0.05 |
| Time production without feedback T7 (180 min) | p≤0.05 | p≤0.05 | ns. | p≤0.05 |
| Time production with feedback T8 (180 min) | ns. | p≤0.05 | ns. | p≤0.05 |

* Only p-values for relevant 2:1 CBD:THC ratio are shown

Available relevant data and p-values of study by Hollister and Gillespie (1975).

| Assessment or measurement | THC | CBD+THC | Statistical significance |
|---|---|---|---|
| Dose of CBD and THC | 20 mg | 40mg + 20 mg | N/A |
| CBD:THC ratio | 0:1 | 2:1 | N/A |
| Peak intensity | 6.7 | 7.0 | N/A |
| ARCI-hallucinogen 2h | 6.0 | 6.6 | N/A |
| ARCI-hallucinogen 4h | 4.5 | 6.0 | N/A |
| ARCI-marihuana 2h | 7.3 | 7.3 | N/A |
| ARCI-marihuana 4h | 7.0 | 8.0 | N/A |

Available relevant data of study by Dalton et al. (1976).

| Assessment or measurement | Placebo | CBD | THC | CBD + THC | Pooled SD |
|---|---|---|---|---|---|
| Dose of CBD and THC | - | 150 µg/kg | 25 µg/kg | 150 µg/kg + 25 µg/kg | - |
| CBD:THC ratio | - | 1:0 | 0:1 | 6:1 | - |
| high rating 0 min - mean | 0.7 | 1.5 | 5.3 | 4.3 | 1.6 |
| high rating 15 min - mean | 0.9 | 1.6 | 5.7 | 4.5 | 1.7 |
| high rating 35 min - mean | 0.9 | 1.5 | 5.1 | 3.9 | 1.8 |
| high rating 55 min - mean | 0.5 | 0.9 | 3.6 | 3.1 | 1.6 |
| high rating 75 min - mean | 0.3 | 0.3 | 2.7 | 2.1 | 1.4 |
| high rating 95 min - mean | 0.3 | 0.2 | 1.7 | 1.2 | 0.9 |
| CMI questions 0 min - mean | 4.7 | 5.7 | 14.1 | 11.1 | 4.0 |
| CMI questions 15 min - mean | 4.4 | 5.5 | 13.7 | 11.1 | 4.8 |
| CMI questions 35 min - mean | 3.1 | 4.9 | 13.7 | 10.3 | 4.8 |

| Assessment or measurement | Placebo | CBD | THC | CBD + THC | Pooled SD |
|---|---|---|---|---|---|
| CMI questions 55 min - mean | 2.9 | 4.9 | 11.1 | 7.7 | 4.8 |
| CMI questions 75 min - mean | 3.0 | 3.3 | 9.5 | 6.7 | 4.5 |
| CMI questions 95 min - mean | 3.1 | 2.8 | 7.5 | 5.9 | 4.3 |
| CMI responses 0 min - mean | 6.6 | 7.9 | 24.6 | 15.7 | 10.4 |
| CMI responses 15 min - mean | 4.7 | 6.6 | 23.4 | 15.4 | 11.0 |
| CMI responses 35 min - mean | 3.6 | 5.6 | 22.7 | 13.3 | 12.0 |
| CMI responses 55 min - mean | 3.8 | 5.9 | 18.1 | 10.1 | 11.9 |
| CMI responses 75 min - mean | 3.8 | 4.2 | 15.3 | 8.1 | 12.1 |
| CMI responses 95 min - mean | 4.1 | 3.7 | 11.4 | 6.9 | 8.7 |

Available relevant p-values for study by Dalton et al. (1976).

| Assessment or measurement | Intersubject variation | CBD vs. placebo | THC vs. placebo | CBD+THC vs.THC |
|---|---|---|---|---|
| high rating 0 min | <0.01 | ns. | <0.01 | <0.05 |
| high rating 15 min | <0.01 | ns. | <0.01 | <0.05 |
| high rating 35 min | <0.05 | ns. | <0.01 | <0.10 |
| high rating 55 min | <0.01 | ns. | <0.01 | ns. |
| high rating 75 min | <0.05 | ns. | <0.01 | ns. |
| high rating 95 min | ns. | ns. | <0.01 | ns. |
| CMI questions 0 min | <0.01 | ns. | <0.01 | <0.10 |
| CMI questions 15 min | <0.01 | ns. | <0.01 | ns. |
| CMI questions 35 min | <0.05 | ns. | <0.01 | <0.05 |
| CMI questions 55 min | <0.10 | ns. | <0.01 | <0.05 |

| Assessment or measurement | Intersubject variation | CBD vs. placebo | THC vs. placebo | CBD+THC vs.THC |
|---|---|---|---|---|
| CMI questions 75 min | <0.10 | ns. | <0.01 | ns. |
| CMI questions 95 min | ns. | ns. | <0.01 | ns. |
| CMI responses 0 min | <0.05 | ns. | <0.01 | <0.10 |
| CMI responses 15 min | <0.10 | ns. | <0.01 | ns. |
| CMI responses 35 min | ns. | ns. | <0.01 | <0.10 |
| CMI responses 55 min | ns. | ns. | <0.01 | ns. |
| CMI responses 75 min | ns. | ns. | <0.05 | ns. |
| CMI responses 95 min | ns. | ns. | <0.05 | ns. |

Available relevant data of study by Zuardi et al. (1982).

| Assessment or measurement | Placebo | CBD | THC | CBD + THC |
|---|---|---|---|---|
| Dose of CBD and THC | - | 1.0 mg/kg | 0.5 mg/kg | 1.0 mg/kg + 0.5 mg/kg |
| CBD:THC ratio | - | 1:0 | 0:1 | 2:1 |
| STAI (most homogenous group) | 0.125 | 0.125 | 15.938 | 8.813 |
| ARCI-Ma (most homogenous group) | - | NR | 18.357 | 9.643 |
| Analogue self-rating scale (Number of participants with changes compared to baseline) | | | | |
| Drowsy - Alert | | Drowsy (1)<br>Alert (5) | Drowsy<br>(5)<br>Alert (0) | Drowsy (4)<br>Alert (2) |
| Feeble - Strong | | Feeble (0)<br>Strong (4) | Feeble (7)<br>Strong (0) | Feeble (3)<br>Strong (2) |
| Incompetent - Proficient | | Incompetent (0)<br>Proficient (4) | Incompetent (6)<br>Proficient (0) | Incompetent (2)<br>Proficient (0) |
| Mentally slow - Quick witted | | Mentally slow (0)<br>Quickwitted (6) | Mentally slow (3)<br>Quickwitted (1) | Mentally slow (2)<br>Quickwitted (3) |
| Muzzy - Clearminded | | Muzzy (0)<br>Clearminded (6) | Muzzy (6)<br>Clearminded (0) | Muzzy (6)<br>Clearminded (1) |
| Discontent - Contented | | Discontent (3)<br>Contented (2) | Discontent (6)<br>Contented (0) | Discontent (4)<br>Contented (0) |
| Troubled - Tranquil | | Troubled (2)<br>Tranquil (3) | Troubled (6)<br>Tranquil (0) | Troubled (4)<br>Tranquil (3) |
| Withdrawn - Gregarious | | Withdrawn (0)<br>Gregarious (3) | Withdrawn (6)<br>Gregarious (0) | Withdrawn (3)<br>Gregarious (2) |

Available relevant data of study by Zuardi et al. (1982) (continued).

| Assessment or measurement | Placebo | CBD | THC | CBD + THC |
|---|---|---|---|---|
| Descriptive summary 0-30 min (number of participants affected) | Sleepiness (2) | - | Difficulty in concentrating (5)<br>Depersonalization (3)<br>Dizziness (3)<br>Change in body image (2)<br>Paresthesia (2)<br>Dry mouth (2)<br>Restlesness (2) | Sleepiness (2) |
| Descriptive summary 30-60 min (number of participants affected) | Sleep (3) | Sleepiness (2) | Difficulty in concentrating (5)<br>Anxiety (5)<br>Hiperacusia (5)<br>Depersonalization (4)<br>Sleep (4)<br>Change in body image (3)<br>Resistance to communication (3)<br>Dizziness (3)<br>Dry mouth (3)<br>Disconnected thoughts (2)<br>Change in perception of time (2)<br>Nausea (2) | Sleep (4) |
| Descriptive summary 60-120 min (number of participants affected) | Sleep (5) | Sleepiness (2) | Hiperacusia (5)<br>Sleep (5)<br>Difficulty in concentrating (4)<br>Resistance to communication (3)<br>Change in body image (2)<br>Disconnected thoughts (2)<br>Anxiety (2)<br>Visions of colored geometric forms with the eyes closed (2)<br>Paranoid ideas (2)<br>Dizziness (2)<br>A sensation of cold (2) | Sleep (7)<br>Difficulty in concentrating (3)<br>Depersonalization (2)<br>Paresthesia (2) |
| Descriptive summary 120-180 min (number of participants affected) | - | - | Resistance to communication (5)<br>Disconnected thoughts (4)<br>Sleep (4)<br>Tiredness (3)<br>Anxiety (2)<br>Dizziness (2) | Sleep (5) |

Available relevant p-values for study by Zuardi et al. (1982).

| Assessment or measurement | CBD vs. baseline | THC vs. baseline | CBD+THC vs. baseline | CBD+THC vs. THC |
|---|---|---|---|---|
| STAI (most homogenous group) | ns. | p≤0.05 | p≤0.05 | NR |
| ARCI-Ma (most homogenous group) | NR | p≤0.05 | p≤0.05 | "Significant" |
| Analogue self-rating scale (Number of participants with changes compared to baseline) | | | | |
| Drowsy - Alert | ns. | ns. | ns. | NR |
| Feeble - Strong | ns. | p<0.02 | ns. | NR |
| Incompetent - Proficient | ns. | p<0.05 | ns. | NR |
| Mentally slow - Quick witted | p<0.05 | ns. | ns. | NR |
| Muzzy - Clearminded | p<0.05 | p<0.05 | ns. | NR |
| Discontent - Contented | ns. | p<0.05 | ns. | NR |
| Troubled - Tranquil | ns. | p<0.05 | ns. | NR |
| Withdrawn - Gregarious | ns. | p<0.05 | ns. | NR |
| Descriptive summary 0-30 min | NR | NR | NR | NR |
| Descriptive summary 30-60 min | NR | NR | NR | NR |
| Descriptive summary 60-120 min | NR | NR | NR | NR |
| Descriptive summary 120-180 min | NR | NR | NR | NR |

Available relevant data of study by Hindocha et al. (2015). **Bolded** values estimated from figures with DigitizeIt-software.

| Assessment or measurement | Placebo | CBD | THC | CBD + THC |
|---|---|---|---|---|
| Dose of CBD and THC | - | 16 mg | 8 mg | 16 mg + 8 mg |
| CBD:THC ratio | - | 1:0 | 0:1 | 2:1 |
| Affect recognition | | | | |
| Affect recognition 20% - Accuracy % - mean (SEM) | **11.6 (0.75)** | **12.9 (1.15)** | **13.9 (1.0)** | **13.0 (0.85)** |
| Affect recognition 40% - Accuracy % - mean (SEM) | **44.9 (1.55)** | **46.0 (1.4)** | 39.75 (4.51) [a] | 43.52 (10.9) [a] |
| Affect recognition 60% - Accuracy % - mean (SEM) | **72 (1.7)** | **75.6 (1.45)** | **73.1 (1.75)** | **71.0 (1.7)** |
| Affect recognition 80% - Accuracy % - mean (SEM) | **76.9 (1.7)** | **78.5 (1.25)** | **77.9 (1.6)** | **75.4 (1.45)** |
| Affect recognition 100% - Accuracy % - mean (SEM) | **79.0 (1.0)** | **80.5 (1.05)** | **77.7 (1.0)** | **76.9 (1.05)** |
| VAS - Stoned (-15 min) - mean (SEM) | **1.10 (0.08)** | **1.10 (0.08)** | **1.10 (0.08)** | **1.10 (0.08)** |
| VAS - Stoned (2 min) - mean (SEM) | **1.57 (0.165)** | **1.97 (0.22)** | **2.82 (0.305)** | **2.63 (0.275)** |
| VAS - Stoned (30 min) - mean (SEM) | **2.28 (0.21)** | **2.16 (0.23)** | **4.20 (0.34)** | **4.16 (0.365)** |
| VAS - Stoned (60 min) - mean (SEM) | **2.22 (0.21)** | **2.11 (0.22)** | **3.76 (0.22)** | **3.99 (0.335)** |
| VAS - Stoned (90 min) - mean (SEM) | **1.80 (0.195)** | **1.89 (0.22)** | **3.06 (0.295)** | **3.10 (0.27)** |
| VAS - Stoned (120 min) - mean (SEM) | **1.74 (0.17)** | **1.61 (0.16)** | **2.89 (0.295)** | **2.55 (0.235)** |
| VAS - Anxiety | - | - | - | - |
| VAS - Alert | - | - | - | - |
| VAS - Happy | - | - | - | - |

a The measure of variation is standard deviation, not standard error of mean.

Available relevant p-values for study by Hindocha et al. (2015)

| Assessment or measurement | CBD vs. Placebo | THC vs. Placebo | CBD+THC vs. placebo | CBD+THC vs. THC |
|---|---|---|---|---|
| Affect recognition | p=0.026 | ns. | ns. | NR |
| Affect recognition 20% | ns. | ns. | ns. | ns. |
| Affect recognition 40% | ns. | p≤0.001 | ns. | p=0.024 |
| Affect recognition 60% | p=0.010 | ns. | ns. | ns. |
| Affect recognition 80% | ns. | ns. | ns. | ns. |
| Affect recognition 100% | ns. | ns. | ns. | ns. |
| VAS - Stoned (-15 min) | ns. | ns. | ns. | ns. |
| VAS - Stoned (2 min) | ns. | p≤0.001 | p≤0.001 | ns. |
| VAS - Stoned (30 min) | ns. | p≤0.001 | p≤0.001 | ns. |
| VAS - Stoned (60 min) | ns. | p≤0.001 | p≤0.001 | ns. |
| VAS - Stoned (90 min) | ns. | p≤0.001 | p≤0.001 | ns. |
| VAS - Stoned (120 min) | ns. | p≤0.001 | p≤0.001 | ns. |
| VAS - Anxiety | ns. | ns. | ns. | NR |
| VAS - Alert | ns. | ns. | ns. | NR |
| VAS - Happy | ns. | ns. | ns. | NR |

Available relevant data of study by Morgan et al. (2018). **Bolded** values estimated from figures with DigitizeIt-software.

| Assessment or measurement | Placebo | CBD | THC | CBD+THC |
|---|---|---|---|---|
| Dose | - | 16 mg | 8 mg | 16 mg + 8 mg |
| CBD:THC ratio | - | 1:0 | 0:1 | 2:1 |
| PSI | - | - | - | - |
| PSI - Subscale - Delusory thinking - mean* | **0.98 (0.24)** | **1.01 (0.25)** | **1.07 (0.27)** | **1.05 (0.26)** |
| PSI - Subscale - Perceptual disorders - mean* | **0.83 (0.27)** | **1.04 (0.25)** | **1.82 (0.36)** | **1.61 (0.34)** |
| PSI - Subscale - Cognitive disorganisation - mean* | **4.89 (0.67)** | **4.64 (0.65)** | **7.06 (0.81)** | **7.14 (0.80)** |
| PSI - Subscale - Anhedonia - mean* | **5.26 (0.54)** | **4.66 (0.56)** | **5.09 (0.49)** | **4.87 (0.53)** |
| PSI - Subscale - Mania - mean* | **3.82 (0.36)** | **3.72 (0.38)** | **4.19 (0.41)** | **4.00 (0.39)** |
| PSI - Subscale - Paranoia - mean* | **0.90 (0.31)** | **0.93 (0.30)** | **1.32 (0.40)** | **1.17 (0.38)** |
| BPRS | - | - | - | - |
| BPRS - Subscale - Positive symptoms* | **6.43 (0.12)** | **6.52 (0.13)** | **6.68 (0.16)** | **6.32 (0.09)** |
| BPRS - Subscale - Negative symptoms* | **4.05 (0.21)** | **4.53 (0.30)** | **4.70 (0.24)** | **4.91 (0.31)** |
| Prose recall | - | - | - | - |
| Prose recall - Immediate* | **9.50 (0.50)** | **10.0 (0.60)** | **8.08 (0.57)** | **8.37 (0.59)** |
| Prose recall - Delayed* | **8.84 (0.55)** | **9.16 (0.60)** | **7.65 (0.56)** | **7.60 (0.60)** |
| Spatial N-Back - Sensitivity* | - | - | - | - |
| Spatial N-Back - Sensitivity - 1-Back* | **2.74 (0.11)** | **2.51 (0.12)** | **2.28 (0.18)** | **2.36 (0.13)** |
| Spatial N-Back - Sensitivity - 2-Back* | **2.17 (0.17)** | **2.19 (0.18)** | **1.83 (0.21)** | **1.92 (0.18)** |
| Spatial N-Back - Reaction time | - | - | - | - |
| Spatial N-Back - Reaction time- 1-Back* | **590 (60)** | **670 (80)** | **800 (100)** | **740 (90)** |
| Spatial N-Back - Reaction time- 2-Back* | **910 (110)** | **920 (100)** | **1140 (140)** | **1020 (120l)** |
| Fluency mean (SE) | 16.63 (0.655) | 14.3 (0.34) | 17.2 (0.68) | 19.0 (0.546) |

| Assessment or measurement | Placebo | CBD | THC | CBD+THC |
|---|---|---|---|---|
| Retain's trailmaking test mean (SE) | 15.76 (0.76) | 14.20 (0.47) | - | - |

* The measure of variation depicted in the figures was ambiguous.

Available relevant p-values for study by Morgan et al. (2018).

| Assessment or measurement | CBD vs. Placebo | THC vs. Placebo | CBD+THC vs. placebo | CBD+THC vs. THC |
|---|---|---|---|---|
| PSI | ns. (p=0.544) | p=0.014 | p=0.022 | NR |
| PSI - Subscale - Delusory thinking | ns. | ns. | ns. | NR |
| PSI - Subscale - Perceptual disorders | ns. | p=0.006 | p=0.005 | NR |
| PSI - Subscale - Cognitive disorganisation | ns. | p=0.008 | p=0.004 | NR |
| PSI - Subscale - Anhedonia | ns. | ns. | ns. | NR |
| PSI - Subscale - Mania | ns. | ns. | ns. | NR |
| PSI - Subscale - Paranoia | ns. | ns. | ns. | NR |
| BPRS | ns. | ns. | ns. | NR |
| BPRS - Subscale - Positive symptoms | ns. | ns. | ns. | NR |
| BPRS - Subscale - Negative symptoms | ns. | p=0.025 | p=0.008 | NR |
| Prose recall | ns. | p=0.031 | p=0.024 | NR |
| Prose recall - Immediate | ns. | p≤0.05 | p≤0.05 | NR |
| Prose recall - Delayed | ns. | p≤0.05 | p≤0.05 | NR |
| Spatial N-Back - Sensitivity | ns. (p=0.532) | p=0.012 | p=0.020 | NR |
| Spatial N-Back - Sensitivity - 1-Back | ns. | ns. | ns. | NR |
| Spatial N-Back - Sensitivity - 2-Back | ns. | ns. | ns. | NR |
| Spatial N-Back - Reaction time | ns. | ns. | ns. | NR |
| Spatial N-Back - Reaction time- 1-Back | ns. | ns. | ns. | NR |
| Spatial N-Back - Reaction time- 2-Back | ns. | ns. | ns. | NR |

| Assessment or measurement | CBD vs. Placebo | THC vs. Placebo | CBD+THC vs. placebo | CBD+THC vs. THC |
|---|---|---|---|---|
| Fluency mean (SE) | ns. | ns. | p=0.005 | NR |
| Retain's trailmaking test mean (SE) | p=0.045 | ns. | ns. | NR |

Available relevant data of study by Woelfi et al. (2020). **Bolded** values estimated from figures with DigitizeIt-software.

| Assessment or measurement | Placebo | CBD | THC | CBD+THC |
|---|---|---|---|---|
| Dose of CBD and THC | - | 800 mg | 20 mg | 800 mg + 20 mg |
| CBD:THC ratio | - | 1:0 | 0:1 | 40:1 |
| EWL category - Performance-related activity - (median) | -3 | -2 | **-5** | -8 |
| EWL category - Performance-related activity - (0 percentile) | -12 | -18 | **-12** | -12 |
| EWL category - Performance-related activity - (25 percentile) | -5 | -7 | **-8.5** | -9 |
| EWL category - Performance-related activity - (75 percentile) | -1 | -1 | **-3.5** | -5 |
| EWL category - Performance-related activity - (100 percentile) | 2 | 8 | **2** | -4 |
| EWL category - Depressiveness - (median) | 0 | 0 | **1** | 1 |
| EWL category - Depressiveness - (0 percentile) | 4 | -4 | **0** | -1 |
| EWL category - Depressiveness - (25 percentile) | 0 | 0 | **0** | 0 |
| EWL category - Depressiveness - (75 percentile) | 1 | 1 | **2** | 6 |
| EWL category - Depressiveness - (100 percentile) | 3 | 3 | **4** | 8 |
| EWL category - Extraversion - (median) | 0 | -1 | **-3** | -3 |
| EWL category - Extraversion - (0 percentile) | -10 | -7 | **-10** | -11 |
| EWL category - Extraversion - (25 percentile) | -2.5 | -3 | **-5.5** | -8 |
| EWL category - Extraversion - (75 percentile) | 1 | 0.5 | **-0.5** | -2 |
| EWL category - Extraversion - (100 percentile) | 6 | 4 | **2** | 0 |

| Assessment or measurement | Placebo | CBD | THC | CBD+THC |
|---|---|---|---|---|
| EWL category - Emotional excitability - (median) | **1** | **-1** | **0** | **2** |
| EWL category - Emotional excitability - (0 percentile) | **-5** | **-3** | **-4** | **-5** |
| EWL category - Emotional excitability - (25 percentile) | **-1** | **-2** | **-1** | **0** |
| EWL category - Emotional excitability - (75 percentile) | **2.5** | **0** | **2** | **4** |
| EWL category - Emotional excitability - (100 percentile) | **6** | **3** | **5** | **10** |
| Digit Symbol Coding Task - (median) | **7** | 6 | 2 | -2 |
| Digit Symbol Coding Task - (0 percentile) | **-2** | -3 | -79 | -27 |
| Digit Symbol Coding Task - (25 percentile) | **1** | 5 | -4.5 | -12.5 |
| Digit Symbol Coding Task - (75 percentile) | **9.5** | 12 | 6 | 7 |
| Digit Symbol Coding Task - (100 percentile) | **22** | 20 | 20 | 11 |
| Letter-Number - Sequencing test - (median) | **0** | 2 | **0** | 0 |
| Letter-Number - Sequencing test - (0 percentile) | **-3** | -2 | **-4** | -4 |
| Letter-Number - Sequencing test - (25 percentile) | **-1** | 0.5 | **-2** | -1.5 |
| Letter-Number - Sequencing test - (75 percentile) | **2.5** | 3 | **1** | 1 |
| Letter-Number - Sequencing test - (100 percentile) | **5** | 4 | **5** | 2 |
| d2 Test of Attention - (median) | 25 | 29 | **15** | -10 |
| d2 Test of Attention - (0 percentile) | -20 | -48 | **-1** | -55 |
| d2 Test of Attention - (25 percentile) | 16 | 10.5 | **3.5** | -25 |
| d2 Test of Attention - (75 percentile) | 33.5 | 35.5 | **21** | 15 |
| d2 Test of Attention - (100 percentile) | 43 | 67 | **23** | 62 |

Available relevant p-values for study by Woelfi et al. (2020).

| Assessment or measurement | CBD vs. Placebo | THC vs. Placebo | THC vs. CBD | CBD+THC vs. placebo | CBD+THC vs. CBD | CBD+THC vs. THC |
|---|---|---|---|---|---|---|
| EWL category - Performance-related activity | ns. | ns. | ns. | p=0.002 | p=0.035 | ns |
| EWL category - Depressiveness | ns. | ns. | ns. | p=0.015 | p=0.026 | ns. |
| EWL category - Extraversion | ns. | ns. | ns. | p=0.013 | p=0.017 | ns. |
| EWL category - Emotional excitability | ns. | ns. | ns. | ns. | ns. | ns. |
| Digit Symbol Coding Task | ns. | ns. | p=0.039 | ns. | p=0.016 | ns. |
| Letter-Number-Sequencing test | ns. | ns. | ns. | ns. | p=0.005 | ns. |
| d2 Test of Attention | ns. | ns. | ns. | p=0.005 | p=0.010 | ns. |

Available relevant data of study by Sainz-Cort et al. (2021). **Bolded** values estimated from figures with DigitizeIt-software.

| Assessment or measurement | Placebo | CBD | THC | CBD+THC |
|---|---|---|---|---|
| Dose of CBD and THC | - | 130 mg | 65 mg | 130 mg + 65 mg |
| CBD:THC ratio | - | 1:0 | 0:1 | 2:1 |
| VAS - Time perception - mean (SD) | 23.69 (38.97) | 26.08 (39.75) | 156.12 (102.30) | 68.43 (59.12) |
| VAS - Change in control of thoughts - mean (SD) | 24.54 (43.42) | 29.86 (51.97) | 164.07 (99.04) | 69.65 (79.61) |
| VAS - Feeling high - mean (SD) | 16.72 (30.88) | 25.92 (34.41) | 210.68 (104.92) | 75.83 (73.20) |
| VAS - Feeling drowsy - mean (SD) | 30.35 (35.65) | 34.09 (49.47) | 85.35 (72.09) | 31.056 (24.73) |
| VAS - Feeling muzzy - mean (SD) | 9.49 (24.39) | 8.50 (16.73) | 88.44 (76.94) | 20.92 (26.53) |
| VAS - Feeling dreamy - mean (SD) | 20.49 (41.24) | 11.22 (21.21) | 84.67 (90.50) | 36.80 (48.35) |
| VAS - Mental slowness - mean (SD) | 20.01 (33.53) | 16.94 (36.16) | 119.29 (93.73) | 52.60 (57.66) |
| VAS - Hearing voices - mean (SD) | 0.42 (1.77) | 0.00 (0) | 17.08 (40.35) | 0.00 (0) |

| Assessment or measurement | Placebo | CBD | THC | CBD+THC |
|---|---|---|---|---|
| VAS - Special meaning - mean (SD) | 10.01 (24.35) | 8.28 (26.55) | 61.29 (68.40) | 27.11 (50.12) |
| VAS - Suspicious ideas or beliefs - mean (SD) | 2.78 (10.23) | 1.37 (5.83) | 20.39 (36.99) | 1.39 (3.89) |
| VAS - Feelings of appetite - mean (SD) | 29.21 (51.94) | 11.00 (35.02) | 55.32 (68.24) | 34.24 (58) |
| VAS - Feelings of hunger - mean (SD) | 22.54 (40.87) | 17.54 (43.00) | 47.06 (61.13) | 31.22 (49.77) |
| PSI - Subscale - Delusional thinking - mean (SD) | 2.44 (3.47) | 1.89 (2.95) | 4.39 (4.42) | 2.89 (3.89) |
| PSI - Subscale - Perceptual distortion - mean (SD) | 2.22 (1.86) | 1.94 (1.98) | 7.06 (4.92) | 4.11 (2.93) |
| PSI - Subscale - Cognitive disorganization - mean (SD) | 3.56 (2.87) | 3.61 (2.79) | 13.78 (8.43) | 6.61 (6.55) |
| PSI - Subscale - Anhedonia - mean (SD) | 4.33 (3.01) | 3.83 (2.57) | 5.72 (3.43) | 4.11 (4.30) |
| PSI - Subscale - Mania - mean (SD) | 4.06 (2.01) | 4.00 (1.71) | 6.67 (3.18) | 5.33 (2.99) |
| PSI - Subscale - Paranoia - mean (SD) | 0.56 (0.92) | 0.39 (0.78) | 1.89 (1.78) | 1.06 (1.30) |
| ARCI - Subscale - Euphoria - mean (SD) | 3.06 (1.92) | 2.78 (2.18) | 3.67 (2.35) | 3.39 (2.28) |
| ARCI - Subscale - Activation - mean (SD) | 1.11 (1.13) | 0.94 (1.59) | 0.83 (1.47) | 0.39 (1.38) |
| ARCI - Subscale - Sedation - mean (SD) | 0.56 (1.20) | 0.61 (1.20) | 2.89 (1.78) | 2.17 (1.72) |
| VAS - high score 15 min - mean (SEM) | **0.35 (0.18)** | **0.63 (0.26)** | **5.75 (0.82)** | **1.57 (1.03)** |
| VAS - high score 25 min - mean (SEM) | **0.65 (0.22)** | **0.67 (0.27)** | **6.00 (0.81)** | **2.91 (1.02)** |
| VAS - high score 35 min - mean (SEM) | **0.62 (0.30)** | **1.00 (0.33)** | **6.00 (0.74)** | **2.58 (1.02)** |
| VAS - high score 45 min - mean (SEM) | **0.55 (0.30)** | **0.71 (0.24)** | **5.88 (0.75)** | **2.05 (1.02)** |
| VAS - high score 55 min - mean (SEM) | **0.26 (0.15)** | **0.62 (0.27)** | **5.15 (0.83)** | **2.21 (1.02)** |
| VAS - high score 65 min - mean (SEM) | **0.34 (0.22)** | **0.55 (0.23)** | **4.58 (0.85)** | **1.42 (1.02)** |
| VAS - high score 75 min - mean (SEM) | **0.07 (0.11)** | **0.54 (0.33)** | **3.98 (0.79)** | **1.46 (1.03)** |

Available relevant p-values for study by Sainz-Cort et al. (2021).

| Assessment or measurement | CBD vs. placebo | THC vs. Placebo | THC vs. CBD | CBD+THC vs. placebo | CBD+THC vs. CBD | CBD+THC vs. THC |
|---|---|---|---|---|---|---|
| VAS - Time perception | ns. (p=0.775) | p<0.001 | p<0.001 | p=0.003 | p=0.007 | p<0.001 |
| VAS - Change in control of thoughts | ns. (p=0.432) | p<0.001 | p<0.001 | p=0.003 | ns. (p=0.027) | p<0.001 |
| VAS - Feeling high | ns. (p=0.471) | p<0.001 | p<0.001 | p<0.001 | p<0.001 | p<0.001 |
| VAS - Feeling drowsy | ns. (p=0.565) | p<0.001 | p=0.004 | ns. (p=0.430) | ns. (p=0.289) | p=0.008 |
| VAS - Feeling muzzy | ns. (p=0.233) | p<0.001 | p<0.001 | ns. (p=0.038) | ns. (p=0.358) | p<0.001 |
| VAS - Feeling dreamy | ns. (p=0.806) | p<0.001 | p<0.001 | ns. (p=0.124) | ns. (p=0.194) | p=0.006 |
| VAS - Mental slowness | ns. (p=0.679) | p<0.001 | p<0.001 | p=0.007 | ns. (p=0.020) | p<0.001 |
| VAS - Hearing voices | ns. (p=0.415) | ns. (p=0.025) | p=0.003 | ns. (p=0.415) | ns. (p=1) | p=0.003 |
| VAS - Special meaning | ns. (p=0.767) | p<0.001 | p<0.001 | ns. (p=0.097) | ns. (p=0.170) | p=0.003 |
| VAS - Suspicious ideas or beliefs | ns. (p=0.284) | p<0.001 | p<0.001 | ns. (p=0.810) | ns. (p=0.192) | p=0.001 |
| VAS - Feelings of appetite | ns. (p=0.736) | p<0.005 | p=0.002 | ns. (p=0.674) | ns. (p=0.450) | ns. (p=0.014) |
| VAS - Feelings of hunger | ns. | ns. | ns. | ns. | ns. | ns. |
| PSI - Subscale - Delusional thinking | ns. (p=0.260) | ns. (p=0.032) | p=0.002 | ns. (p=0.808) | ns. (p=0.172) | ns. (p=0.056) |
| PSI - Subscale - Perceptual distortion | ns. (p=0.812) | p<0.001 | p<0.001 | ns. (p=0.009) | p=0.005 | ns. (p=0.239) |
| PSI - Subscale - Cognitive disorganization | ns. (p=0.932) | p<0.001 | p<0.001 | ns. (p=0.210) | ns. (p=0.241) | p<0.001 |
| PSI - Subscale - Anhedonia | ns. | ns. | ns. | ns. | ns. | ns. |
| PSI - Subscale - Mania | ns. (p=0.770) | p=0.007 | p=0.003 | ns. (p=0.113) | ns. (p=0.062) | ns. (p=0.246) |
| PSI - Subscale - Paranoia | ns. (p=0.723) | p=0.002 | p=0.001 | ns. (p=0.080) | ns. (p=0.037) | ns. (p=0.160) |

| Assessment or measurement | CBD vs. placebo | THC vs. Placebo | THC vs. CBD | CBD+THC vs. placebo | CBD+THC vs. CBD | CBD+THC vs. THC |
|---|---|---|---|---|---|---|
| ARCI - Subscale - Euphoria | ns. | ns. | ns. | ns. | ns. | ns. |
| ARCI - Subscale - Activation | ns. | ns. | ns. | ns. | ns. | ns. |
| ARCI - Subscale - Sedation | ns. (p=0.567) | p<0.001 | p<0.001 | p<0.001 | p=0.002 | ns. (p=0.039) |

Available relevant data of study by Englund et al. (2023). EMM = estimated marginal mean.

| Assessment or measurement | Baseline | THC | CBD+THC | CBD+THC | CBD+THC |
|---|---|---|---|---|---|
| Dose of CBD and THC | - | 10 mg | 10 mg + 10 mg | 20 mg + 10 mg | 30 mg + 10 mg |
| CBD:THC ratio | - | 0:1 | 1:1 | 2:1 | 3:1 |
| HVLT - Immediate recall - EMM (SE) | 29.3 (0.647) | 26.1 (0.647) | 25.7 (0.647) | 25.1 (0.647) | 26.4 (0.647) |
| HVLT - Delayed recall - EMM (SE) | 10.50 (0.314) | 9.41 (0.314) | 9.26 (0.314) | 9.09 (0.314) | 9.39 (0.314) |
| HVLT - Retention - EMM (SE) | 95.2 (2.14) | 91.3 (2.14) | 91.2 (2.14) | 88.8 (2.14) | 88.9 (2.14) |
| HVLT - Immediate repetitions - EMM (SE) | 2.39 (0.325) | 1.80 (0.325) | 1.24 (0.325) | 1.13 (0.325) | 1.61 (0.325) |
| HVLT - Delayed repetitions - EMM (SE) | 0.44 (0.084) | 0.22 (0.084) | 0.09 (0.084) | 0.20 (0.084) | 0.17 (0.084) |
| HVLT - Immediate intrusions - EMM (SE) | 0.74 (0.266) | 1.57 (0.266) | 1.57 (0.266) | 1.41 (0.266) | 1.78 (0.266) |
| HVLT - Delayed intrusions - EMM (SE) | 0.30 (0.135) | 0.85 (0.135) | 0.70 (0.135) | 0.63 (0.135) | 0.80 (0.135) |
| Forward digit span - EMM (SE) | 7.26 (0.186) | 6.54 (0.186) | 6.30 (0.186) | 6.30 (0.186) | 6.50 (0.186) |
| Reverse digit span - EMM (SE) | 5.47 (0.159) | 5.00 (0.159) | 4.93 (0.159) | 4.91 (0.159) | 4.93 (0.159) |
| Spatial N-back - 0 back - EMM (SE) | 0.972 (0.004) | 0.969 (0.004) | 0.968 (0.004) | 0.971 (0.004) | 0.977 (0.004) |

| Assessment or measurement | Baseline | THC | CBD+THC | CBD+THC | CBD+THC |
|---|---|---|---|---|---|
| Spatial N-back - 1 back - EMM (SE) | 0.927 (0.013) | 0.901 (0.013) | 0.873 (0.013) | 0.904 (0.013) | 0.885 (0.013) |
| Spatial N-back - 2 back - EMM (SE) | 0.799 (0.026) | 0.748 (0.026) | 0.761 (0.026) | 0.745 (0.026) | 0.767 (0.026) |
| PANSS-P | 7.04 (0.317) | 8.96 (0.317) | 8.61 (0.317) | 9.35 (0.317) | 8.70 (0.317) |
| SSPS | 10.1 (0.116) | 10.2 (0.116) | 10.5 (0.116) | 10.5 (0.116) | 10.1 (0.116) |
| CAPE-state | 1.33 (0.669) | 4.50 (0.674) | 4.24 (0.684) | 4.80 (0.674) | 5.17 (0.669) |
| PSI | 7.46 (1.96) | 21.91 (1.90) | 22.5 (1.88) | 24.1 (1.90) | 24.1 (1.88) |
| VAS - Drug effects pleasurable - Baseline - mean (SD) | - | 0.21 (0.730) | 0.34 (1.06) | 0.29 (0.87) | 0.30 (1.01) |
| VAS - Drug effects pleasurable - Peak effects - EMM (SE) | - | 6.74 (0.328) | 6.38 (0.328) | 6.26 (0.328) | 6.54 (0.328) |
| VAS - Drug effects pleasurable - AUC - EMM (SE) | - | 21.6 (.01) | 20.6 (1.0) | 19.2 (1.0) | 20.7 (1.0) |
| VAS - Dry mouth - Baseline - mean (SD) | - | 0.56 (0.92) | 0.50 (1.08) | 0.58 (1.19) | 0.40 (0.90) |
| VAS - Dry mouth - Peak effects - EMM (SE) | - | 3.66 (0.412) | 3.70 (0.412) | 3.21 (0.412) | 3.69 (0.412) |
| VAS - Dry mouth - AUC - EMM (SE) | - | 10.3 (1.14) | 10.8 (1.14) | 10.3 (1.14) | 11.9 (1.14) |
| VAS - Enhanced colour perception - Baseline - mean (SD) | - | 0.10 (0.17) | 0.13 (0.30) | 0.09 (0.22) | 0.18 (0.70) |
| VAS - Enhanced colour perception - Peak effects - EMM (SE) | - | 2.96 (0.451) | 3.03 (0.451) | 3.34 (0.451) | 3.69 (0.451) |
| VAS - Enhanced colour perception - AUC - EMM (SE) | - | 8.83 (1.27) | 9.44 (1.27) | 9.55 (1.27) | 10.97 (1.27) |
| VAS - Enhanced sound perception - Baseline - mean (SD) | - | 0.10 (0.27) | 0.08 (0.17) | 0.06 (0.15) | 0.18 (0.69) |

| Assessment or measurement | Baseline | THC | CBD+THC | CBD+THC | CBD+THC |
|---|---|---|---|---|---|
| VAS - Enhanced sound perception - Peak effects - EMM (SE) | - | 4.08 (0.416) | 3.94 (0.416) | 4.46 (0.416) | 4.87 (0.416) |
| VAS - Enhanced sound perception - AUC - EMM (SE) | - | 11.9 (1.21) | 12.1 (1.21) | 12.7 (1.21) | 14.7 (1.21) |
| VAS - Feel anxious - Baseline - mean (SD) | - | 0.60 (0.81) | 0.72 (0.97) | 0.56 (0.91) | 0.45 (0.68) |
| VAS - Feel anxious - Peak effects - EMM (SE) | - | 1.45 (0.292) | 0.95 (0.292) | 1.56 (0.292) | 1.42 (0.292) |
| VAS - Feel anxious - AUC - EMM (SE) | - | 3.10 (0.885) | 2.90 (0.885) | 4.71 (0.885) | 4.41 (0.885) |
| VAS - Feel calm and relaxed - Baseline - mean (SD) | - | 5.16 (2.69) | 4.85 (2.43) | 5.31 (2.44) | 5.66 (2.40) |
| VAS - Feel calm and relaxed - Peak effects - EMM (SE) | - | 1.34 (0.451) | 1.69 (0.451) | 0.75 (0.451) | 0.61 (0.451) |
| VAS - Feel calm and relaxed - AUC - EMM (SE) | - | 3.32 (1.41) | 4.45 (1.41) | 1.17 (1.41) | 1.00 (1.41) |
| VAS - Feel drug effect - Baseline - mean (SD) | - | 0.06 (0.15) | 0.05 (0.13) | 0.04 (0.09) | 0.07 (0.18) |
| VAS - Feel drug effect - Peak effects - EMM (SE) | - | 7.55 (0.216) | 7.46 (0.216) | 7.49 (0.216) | 7.80 (0.216) |
| VAS - Feel drug effect - AUC - EMM (SE) | - | 20.9 (0.693) | 21.7 (0.693) | 21.5 (0.693) | 21.8 (0.693) |
| VAS - Feel high - Baseline - mean (SD) | - | 0.08 (0.16) | 0.08 (0.15) | 0.08 (0.17) | 0.07 (0.16) |
| VAS - Feel high - Peak effects - EMM (SE) | - | 7.28 (0.243) | 7.49 (0.243) | 7.42 (0.243) | 7.56 (0.243) |
| VAS - Feel high - AUC - EMM (SE) | - | 19.9 (0.737) | 21.2 (0.737) | 20.9 (0.737) | 21.7 (0.737) |
| VAS - Feel paranoid – Baseline - mean (SD) | - | 0.14 (0.26) | 0.17 (0.31) | 0.17 (0.48) | 0.10 (0.17) |
| VAS - Feel paranoid - Peak effects - EMM (SE) | - | 1.14 (0.264) | 1.23 (0.264) | 1.35 (0.267) | 1.02 (0.261) |

| Assessment or measurement | Baseline | THC | CBD+THC | CBD+THC | CBD+THC |
|---|---|---|---|---|---|
| VAS - Feel paranoid - AUC - EMM (SE) | - | 30.7 (0.822) | 4.25 (0.822) | 4.87 (0.830) | 3.49 (0.813) |
| VAS - Feel stoned - Baseline - mean (SD) | - | 0.09 (0.17) | 0.08 (0.14) | 0.08 (0.14) | 0.07 (0.15) |
| VAS - Feel stoned - Peak effects - EMM (SE) | - | 6.80 (0.31) | 6.84 (0.31) | 6.83 (0.31) | 6.95 (0.31) |
| VAS - Feel stoned - AUC - EMM (SE) | - | 18.5 (0.936) | 19.7 (0.936) | 19.4 (0.936) | 20.1 (0.936) |
| VAS - Feel tired - Baseline - mean (SD) | - | 1.41 (1.53) | 1.28 (1.31) | 1.59 (1.70) | 1.43 (1.61) |
| VAS - Feel tired - Peak effects - EMM (SE) | - | 2.51 (0.372) | 2.74 (0.372) | 2.56 (0.372) | 3.04 (0.372) |
| VAS - Feel tired - AUC - EMM (SE) | - | 8.60 (1.08) | 9.27 (1.08) | 10.00 (1.08) | 11.18 (1.08) |
| VAS - Like drug effect - Baseline - mean (SD) | - | 0.16 (0.70) | 0.30 (0.99) | 0.15 (0.49) | 0.17 (0.75) |
| VAS - Like drug effect - Peak effects - EMM (SE) | - | 7.06 (0.315) | 6.83 (0.315) | 6.32 (0.315) | 6.79 (0.315) |
| VAS - Like drug effect - AUC - EMM (SE) | - | 21.7 (0.972) | 20.9 (0.972) | 19.5 (0.972) | 21.4 (0.972) |
| VAS - Mentally impaired - Baseline - mean (SD) | - | 0.18 (0.40) | 0.26 (0.50) | 0.17 (0.44) | 0.33 (0.88) |
| VAS - Mentally impaired - Peak effects - EMM (SE) | - | 4.58 (0.394) | 4.81 (0.394) | 4.67 (0.394) | 5.38 (0.394) |
| VAS - Mentally impaired - AUC - EMM (SE) | - | 13.2 (1.05) | 14.0 (1.05) | 14.8 (1.05) | 15.9 (1.05) |
| VAS - Want alcohol - Baseline - mean (SD) | - | 0.45 (0.80) | 0.41 (0.93) | 0.26 (0.48) | 0.41 (1.32) |
| VAS - Want alcohol - Peak effects - EMM (SE) | - | 0.57 (0.234) | 0.54 (0.234) | 0.87 (0.234) | 0.57 (0.234) |
| VAS - Want alcohol - AUC - EMM (SE) | - | 2.39 (0.775) | 1.99 (0.775) | 2.28 (0.775) | 2.03 (0.775) |

| Assessment or measurement | Baseline | THC | CBD+THC | CBD+THC | CBD+THC |
|---|---|---|---|---|---|
| VAS - Want food - Baseline - mean (SD) | - | 1.31 (1.43) | 1.49 (1.81) | 1.86 (1.93) | 1.54 (1.36) |
| VAS - Want food - Peak effects - EMM (SE) | - | 2.10 (0.367) | 2.39 (0.367) | 1.76 (0.367) | 2.51 (0.367) |
| VAS - Want food - AUC - EMM (SE) | - | 2.39 (0.775) | 1.99 (0.775) | 2.28 (0.775) | 2.03 (0.775) |
| VAS - Want more drug - Baseline - mean (SD) | - | 0.72 (1.93) | 0.57 (1.42) | 0.66 (1.61) | 0.59 (1.61) |
| VAS - Want more drug - Peak effects - EMM (SE) | - | 1.91 (0.431) | 1.94 (0.431) | 1.58 (0.431) | 1.85 (0.431) |
| VAS - Want more drug - AUC - EMM (SE) | - | 6.43 (1.32) | 6.77 (1.32) | 5.02 (1.32) | 5.92 (1.32) |
| Pleasurable responses - Chocolate | - | 2.31 (1.93) | 2.67 (1.64) | 1.92 (2.03) | 2.63 (1.98) |
| Pleasurable responses - Music | - | 2.25 (2.14) | 2.09 (2.11) | 2.51 (1.71) | 2.03 (2.10) |

Available relevant p-values for study by Englund et al. (2023).

| Assessment or measurement | THC vs. baseline | CBD+THC (1:1) vs. THC | CBD+THC (2:1) vs. THC | CBD+THC (3:1) vs. THC |
|---|---|---|---|---|
| HVLT - Immediate recall | p=2·71x10-6 | ns. (p=0.811) | ns. (p=0.273) | ns. (p=0.933) |
| HVLT - Delayed recall | p=0·001 | ns. (p=0.969) | ns. (p=0.765) | ns. (p=1.000) |
| HVLT - Retention | ns. | ns. (p=1.000) | ns. (p=0.812) | ns. (p=0.824) |
| HVLT - Immediate repetitions | ns. | ns. (p=0.299) | ns. (p=0.160) | ns. (p=0.929) |
| HVLT - Delayed repetitions | ns. | ns. (p=0.578) | ns. (p=0.997) | ns. (p=0.974) |
| HVLT - Immediate intrusions | p=4·02x10-4 | ns. (p=1.000) | ns. (p=0.972) | ns. (p=0.924) |
| HVLT - Delayed intrusions | p=0·002 | ns. (p=0.835) | ns. (p=0.628) | ns. (p=0.995) |
| Forward digit span | p=0·002 | ns. (p=0.588) | ns. (p=0.588) | ns. (p=0.996) |

| Assessment or measurement | THC vs. baseline | CBD+THC (1:1) vs. THC | CBD+THC (2:1) vs. THC | CBD+THC (3:1) vs. THC |
|---|---|---|---|---|
| Reverse digit span | ns. | ns. (p=0.982) | ns. (p=0.960) | ns. (p=0.982) |
| Spatial N-back - 0 back | ns. | ns. (p=1.000) | ns. (p=0.454) | ns. (p=0.315) |
| Spatial N-back - 1 back | ns. | ns. (p=0.646) | ns. (p=0.914) | ns. (p=0.955) |
| Spatial N-back - 2 back | ns. | ns. (p=0.646) | ns. (p=0.914) | ns. (p=0.955) |
| PANSS-P | p=2.41x10-5 | ns. (p=0.264) | ns. (p=0.995) | ns. (p=0.991) |
| SSPS | ns. (p=0.279) | ns. (p=0.326) | ns. (p=0.476) | ns. (p=0.953) |
| CAPE-state | p=0.0002 | ns. (p=0.988) | ns. (p=0.962) | ns. (p=0.792) |
| PSI | p=5.025x10-9 | ns. (p=0.874) | ns. (p=0.846) | ns. (p=0.993) |
| VAS - Drug effects pleasurable - Baseline | - | - | - | - |
| VAS - Drug effects pleasurable - Peak effects | - | ns. (p=0.683) | ns. (p=0.437) | ns. (p=0.929) |
| VAS - Drug effects pleasurable - AUC | - | ns. (p=0.778) | ns. (p=0.099) | ns. (p=0.818) |
| VAS - Dry mouth - Baseline | - | - | - | - |
| VAS - Dry mouth - Peak effects | - | ns. (p=1.000) | ns. (p=0.758) | ns. (p=1.000) |
| VAS - Dry mouth - AUC | - | ns. (p=0.969) | ns. (p=1.000) | ns. (p=0.539) |
| VAS - Enhanced colour perception - Baseline | - | - | - | - |
| VAS - Enhanced colour perception - Peak effects | - | ns. (p=0.999) | ns. (p=0.838) | ns. (p=0.371) |
| VAS - Enhanced colour perception - AUC | - | ns. (p=0.933) | ns. (p=0.898) | ns. (p=0.164) |
| VAS - Enhanced sound perception - Baseline | - | - | - | - |
| VAS - Enhanced sound perception - Peak effects | - | ns. (p=0.990) | ns. (p=0.815) | ns. (p=0.274) |
| VAS - Enhanced sound perception - AUC | - | ns. (p=0.997) | ns. (p=0.900) | ns. (p=0.044) |
| VAS - Feel anxious - Baseline | - | - | - | - |

| Assessment or measurement | THC vs. baseline | CBD+THC (1:1) vs. THC | CBD+THC (2:1) vs. THC | CBD+THC (3:1) vs. THC |
|---|---|---|---|---|
| VAS - Feel anxious - Peak effects | - | ns. (p=0.495) | ns. (p=0.989) | ns. (p=1.000) |
| VAS - Feel anxious - AUC | - | ns. (p=0.997) | ns. (p=0.374) | ns. (p=0.555) |
| VAS - Feel calm and relaxed - Baseline | - | - | - | - |
| VAS - Feel calm and relaxed - Peak effects | - | ns. (p=0.910) | ns. (p=0.667) | ns. (p=0.501) |
| VAS - Feel calm and relaxed - AUC | - | ns. (p=0.878) | ns. (p=0.489) | ns. (p=0.420) |
| VAS - Feel drug effect - Baseline | - | - | - | - |
| VAS - Feel drug effect - Peak effects | - | ns. (p=0.978) | ns. (p=0.994) | ns. (p=0.717) |
| VAS - Feel drug effect - AUC | - | ns. (p=0.568) | ns. (p=0.787) | ns. (p=0.498) |
| VAS - Feel high - Baseline | - | - | - | - |
| VAS - Feel high - Peak effects | - | ns. (p=0.798) | ns. (p=0.938) | ns. (p=0.624) |
| VAS - Feel high - AUC | - | ns. (p=0.179) | ns. (p=0.438) | ns. (p=0.031) |
| VAS - Feel paranoid - Baseline | - | - | - | - |
| VAS - Feel paranoid - Peak effects | - | ns. (p=0.989) | ns. (p=0.896) | ns. (p=0.979) |
| VAS - Feel paranoid - AUC | - | ns. (p=0.559) | ns. (p=0.200) | ns. (p=0.967) |
| VAS - Feel stoned - Baseline | - | - | - | - |
| VAS - Feel stoned - Peak effects | - | ns. (p=0.999) | ns. (p=1.000) | ns. (p=0.971) |
| VAS - Feel stoned - AUC | - | ns. (p=0.465) | ns. (p=0.663) | ns. (p=0.227) |
| VAS - Feel tired - Baseline | - | - | - | - |
| VAS - Feel tired - Peak effects | - | ns. (p=0.955) | ns. (p=1.000) | ns. (p=0.636) |
| VAS - Feel tired - AUC | - | ns. (p=0.948) | ns. (p=0.667) | ns. (p=0.159) |
| VAS - Like drug effect - Baseline | - | - | - | - |
| VAS - Like drug effect - Peak effects | - | ns. (p=0.923) | ns. (p=0.192) | ns. (p=0.882) |
| VAS - Like drug effect - AUC | - | ns. (p=0.872) | ns. (p=0.192) | ns. (p=0.991) |
| VAS - Mentally impaired - Baseline | - | - | - | - |

| Assessment or measurement | THC vs. baseline | CBD+THC (1:1) vs. THC | CBD+THC (2:1) vs. THC | CBD+THC (3:1) vs. THC |
|---|---|---|---|---|
| VAS - Mentally impaired - Peak effects | - | ns. (p=0.929) | ns. (p=0.995) | ns. (p=0.146) |
| VAS - Mentally impaired - AUC | - | ns. (p=0.869) | ns. (p=0.314) | ns. (p=0.024) |
| VAS - Want alcohol - Baseline | - | - | - | - |
| VAS - Want alcohol - Peak effects | - | ns. (p=0.999) | ns. (p=0.651) | ns. (p=1.000) |
| VAS - Want alcohol - AUC | - | ns. (p=0.964) | ns. (p=0.999) | ns. (p=0.975) |
| VAS - Want food - Baseline mean | - | - | - | - |
| VAS - Want food - Peak effects | - | ns. (p=0.800) | ns. (p=0.501) | ns. (p=0.993) |
| VAS - Want food - AUC | - | ns. (p=0.915) | ns. (p=0.757) | ns. (p=0.880) |
| VAS - Want more drug - Baseline | - | - | - | - |
| VAS - Want more drug - Peak effects | - | ns. (p=1.000) | ns. (p=0.856) | ns. (p=0.999) |
| VAS - Want more drug - AUC | - | ns. (p=0.991) | ns. (p=0.611) | ns. (p=0.970) |
| Pleasurable responses - Chocolate | - | ns. (p=0.713) | ns. (p=0.670) | ns. (p=0.769) |
| Pleasurable responses - Music | - | ns. (p=0.971) | ns. (p=0.871) | ns. (p=0.924) |

Available relevant data of study by Lawn et al. (2023). Adult data only.

| Assessment or measurement | THC vs. placebo | CBD+THC vs. placebo | CBD+THC vs. THC |
|---|---|---|---|
| Dose of CBD and THC | - | 0.107 mg/kg | 0.320 mg/kg + 0.107 mg/kg |
| CBD:THC ratio | - | 0:1 | 3:1 |
| VAS - Feel drug effect (20 min) - mean (SD) | 1.625 (1.952) | 8.208 (1.444) | 8.417 (1.213) |
| VAS - Feel drug effect (20 min) - [min-max] | 0-6 | 5-10 | 6-10 |
| Prose recall - Delayed - mean (SD) | 9.291 (3.193) | 6.063 (3.405) | 5.833 (2.721) |
| Prose recall - Delayed - [min-max] | 3-14 | 1-11.5 | 1-11 |

| Assessment or measurement | THC vs. placebo | CBD+THC vs. placebo | CBD+THC vs. THC |
|---|---|---|---|
| PSI - Total - mean (SD) | 10.875 (7.279) | 19.375 (9.011) | 24.083 (10.219) |
| PSI - Total - [min-max] | 2-35 | 2-37 | 5-45 |
| PSI - Subscale - Cognitive disorganisation - mean (SD) | 1.96 (2.71) | 6.50 (4.31) | 8.92 (4.90) |
| PSI - Subscale - Cognitive disorganisation - median | 1 | 7 | 9.5 |
| PSI - Subscale - Cognitive disorganisation - min-max | 0-12 | 0-14 | 0-17 |
| PSI - Subscale - Perceptual distortion - mean (SD) | 1.08 (2.04) | 2.50 (2.02) | 3.50 (2.15) |
| PSI - Subscale - Perceptual distortion - median | 0 | 2.5 | 3.5 |
| PSI - Subscale - Perceptual distortion - min-max | 0-7 | 0-7 | 0-8 |
| PSI - Subscale - Delusory thinking - mean (SD) | 1.17 (2.50) | 1.54 (2.02) | 1.96 (2.63) |
| PSI - Subscale - Delusory thinking - median | 0.5 | 1 | 1 |
| PSI - Subscale - Delusory thinking - min-max | 0-12 | 0-7 | 0-10 |
| PSI - Subscale – Anhedonia - mean (SD) | 3.71 (2.65) | 4.88 (2.89) | 4.25 (2.67) |
| PSI - Subscale – Anhedonia - median | 3 | 4.5 | 5 |
| PSI - Subscale – Anhedonia - min-max | 0-10 | 0-10 | 0-10 |
| PSI - Subscale – Paranoia - mean (SD) | 0.29 (0.81) | 0.38 (0.65) | 1.00 (2.02) |
| PSI - Subscale – Paranoia - median | 0 | 0 | 0 |
| PSI - Subscale – Paranoia - min-max | 0-3 | 0-2 | 0-8 |
| PSI - Subscale – Mania - mean (SD) | 2.67 (1.43) | 3.58 (2.04) | 4.46 (2.08) |
| PSI - Subscale – Mania - median | 3 | 4 | 5 |
| PSI - Subscale – Mania - min-max | 0-6 | 0-7 | 0-8 |
| PANSS - Subscale - Positive - mean (SD) | 7.33 (0.82) | 9.96 (3.03) | 10.83 (2.10) |
| PANSS - Subscale - Positive - median | 7 | 10 | 10 |
| PANSS - Subscale - Positive - min-max | 7-10 | 7-19 | 8-15 |
| PANSS - Subscale - Negative - mean (SD) | 7.08 (0.41) | 7.42 (0.97) | 8.00 (1.41) |

| Assessment or measurement | THC vs. placebo | CBD+THC vs. placebo | CBD+THC vs. THC |
|---|---|---|---|
| PANSS - Subscale - Negative - median | 7 | 7 | 7.5 |
| PANSS - Subscale - Negative - min-max | 7-9 | 7-11 | 7-13 |
| PANSS - Pos. - Clinically significant reaction - Yes - n (%) | 1 (4.2%) | 14 (58.3%) | 16 (66.7%) |
| PANSS - Pos. - Clinically significant reaction - No - n (%) | 23 (95.8%) | 10 (41.7%) | 8 (36.4%) |
| PANSS - Neg. - Clinically significant reaction - Yes - n (%) | 0 (0%) | 1 (4.2%) | 2 (8.3%) |
| PANSS - Neg. - Clinically significant reaction - No - n (%) | 24 (100%) | 23 (95.8%) | 22 (91.7%) |

Available relevant data of study by Lawn et al. (2023). Combined adolescent and adult data. MD = Mean difference.

| Assessment or measurement | THC vs. placebo | CBD+THC vs. placebo | CBD+THC vs. THC |
|---|---|---|---|
| VAS - Feel drug effect (20 min only) - (MD) (95%CI) | 6.292 (5.343, 7.240) | 6.813 (5.964, 7.661) | 0.521 (-0.121, 1.163) |
| VAS - Feel drug effect (20min-180min) | 4.552 | 5.12 | 0.568 |
| VAS - Feel drug effect - AUC | - | - | - |
| VAS - Feel drug effect - Peak effect | - | - | - |
| VAS - Like Drug effect (20min-180min) | - | - | - |
| VAS - Like Drug effect - AUC | - | - | - |
| VAS - Like Drug effect - Peak effect | - | - | - |
| VAS - Dislike drug effect (20min-180min) | - | - | - |
| VAS - Dislike drug effect - AUC | - | - | - |
| VAS - Dislike drug effect - Peak effect | - | - | - |
| VAS - Anxious (-5min-180min) | - | - | - |

| Assessment or measurement | THC vs. placebo | CBD+THC vs. placebo | CBD+THC vs. THC |
|---|---|---|---|
| VAS - Anxious - AUC | - | - | - |
| VAS - Anxious - Peak effect | - | - | - |
| VAS - Paranoid (-5min-180min) | - | - | - |
| VAS - Paranoid - AUC | - | - | - |
| VAS - Paranoid - Peak effect | - | - | - |
| VAS - Happy (-5min-180min) | - | - | - |
| VAS - Happy - AUC | - | - | - |
| VAS - Happy - Peak effect | - | - | - |
| VAS - Want cannabis (-5min-180min) | - | - | - |
| VAS - Want cannabis - AUC | - | - | - |
| VAS - Want cannabis - Peak effect | - | - | - |
| Prose recall - Immediate - (MD) | 3.229 | 3.573 | -0.344 |
| Prose recall - Delayed - (MD) (95%CI) | -2.740 (-4.059, -1.420) | -2.896 (-4.130, -1.662) | 0.156 (-1.069, 1.381) |
| Prose recall - Immediate and delayed | - | - | - |
| PSI - Total - (MD) (95%CI) | 7.771 (2.844, 12.698) | 10.792 (6.172, 15.411) | –3.021 (−6.954, 0.912) |
| PSI - Cognitive disorganisation - (MD) | 3.938 | 5.833 | 1.896 |
| PSI - Perceptual distortion - (MD) | 1.667 | 2.146 | 0.479 |
| PSI - Delusory thinking - (MD) | - | - | - |
| PSI – Anhedonia - (MD) | - | - | - |
| PSI – Paranoia - (MD) | 0.333 | 0.625 | 0.292 |
| PSI – Mania - (MD) | 0.750 | 1.250 | 0.500 |
| PANSS - Subscale - Positive - (MD) (95%CI) | 2.667 (1.503, 3.831) | 3.417 (2.493, 4.341) | -0.750 (-1.899, 0.399) |
| PANSS - Subscale - Negative - (MD) (95%CI) | 0.646 (0.138, 1.154) | 0.958 (0.384, 1.532) | -0.312 (-0.908, 0.283) |

Available relevant p-values for study by Lawn et al. (2023). P-values were not reported for adult-only data and only available for combined adolescent and adult data.

| Assessment or measurement | Adolescents vs. adults (age*Drug) | THC vs. Placebo | CBD+THC vs. placebo | CBD+THC vs. THC |
|---|---|---|---|---|
| VAS - Feel drug effect (20 min only) | ns. (p=0.547) | p<0.001 | p<0.001 | ns. (p=0.149) |
| VAS - Feel drug effect (20min-180min) | ns. (p=0.353) | p<0.001 | p<0.001[a] | p=0.007[a] |
| VAS - Feel drug effect - AUC | ns. (p=0.321) | "significant" | "significant" | "significant" |
| VAS - Feel drug effect - Peak effect | ns. (p=0.673) | "significant" | "significant" | ns. |
| VAS - Like Drug effect (20min-180min) | ns. (p=0.609) | p<0.001 | p<0.001[a] | ns.[a] |
| VAS - Like Drug effect - AUC | ns. (p=0.710) | "significant" | "significant" | ns. |
| VAS - Like Drug effect - Peak effect | ns. (p=0.656) | "significant" | "significant" | ns. |
| VAS - Dislike drug effect (20min-180min) | ns. (p=0.384) | ns. | ns.[a] | ns.[a] |
| VAS - Dislike drug effect - AUC | ns. (p=0.582) | ns. | ns. | ns. |
| VAS - Dislike drug effect - Peak effect | ns. (p=0.071) | ns. | "significant" | ns. |
| VAS - Anxious (-5min-180min) | ns. (p=0.062) | p<0.001 | p<0.001[a] | p=0.989[a] |
| VAS - Anxious - AUC | ns. (p=0.052) | "significant" | "significant" | ns |
| VAS - Anxious - Peak effect | ns. (p=0.220) | "significant" | "significant" | ns |
| VAS - Paranoid (-5min-180min) | ns. (p=0.998) | p=0.008 | p=0.002[a] | ns.[a] |
| VAS - Paranoid - AUC | ns. (p=0.899) | "significant" | "significant" | ns. |
| VAS - Paranoid - Peak effect | ns. (p=0.946) | "significant" | "significant" | ns. |
| VAS - Happy (-5min-180min) | p=0.012 | ns. | ns.[a] | ns.[a] |
| VAS - Happy - AUC | p=0.019 | ns. | ns. | ns. |
| VAS - Happy - Peak effect | ns. (p=0.073) | "significant" | ns. | ns. |
| VAS - Want cannabis (-5min-180min) | ns. (p=0.441) | ns. | ns.[a] | ns.[a] |
| VAS - Want cannabis - AUC | ns. (p=0.543) | ns. | ns. | ns. |
| VAS - Want cannabis - Peak effect | ns. (p=0.455) | ns. | ns. | ns. |

| Assessment or measurement | Adolescents vs. adults (age*Drug) | THC vs. Placebo | CBD+THC vs. placebo | CBD+THC vs. THC |
|---|---|---|---|---|
| Prose recall - Immediate | ns. (p=0.236) | p<0.001 | p<0.001 | ns. (p=1) |
| Prose recall - Delayed | ns. (p=0.486) | p<0.001 | p<0.001 | ns. (p=1) |
| Prose recall - Immediate and delayed | ns. (p=0.711) | "significant" | "significant" | ns. |
| PSI - Total | ns. (p=0.932) | p=0.001 | p<0.001 | ns. (p=0.188) |
| PSI - Cognitive disorganisation | ns. (p=0.294) | p<0.001 | p<0.001 | p=0.003 |
| PSI - Perceptual distortion | ns. (p=0.485) | p=0.002 | p<0.001 | ns. (p=0.602) |
| PSI - Delusory thinking | ns. (p=0.924) | ns. | ns. | ns. |
| PSI - Anhedonia | ns. (p=0.313) | ns. | ns. | ns. |
| PSI - Paranoia | ns. (p=0.383) | ns. (p=0.382) | ns. (p=0.083) | ns. (p=0.711) |
| PSI - Mania | ns. (p=0.289) | ns. (p=0.134) | p=0.002 | ns. (p=0.463) |
| PANSS - Subscale - Positive | ns. (p=0.958) | p<0.001 | p<0.001 | ns. (p=0.355) |
| PANSS - Subscale - Negative | ns. (p=0.327) | p=0.008 | p<0.001 | ns. (p=0.596) |

a Data was missing for one adult in CBD+THC intervention at t=180 minutes

Combined adolescent and adult analyses assumed valid for adults-only interpretation when age*drug p>0.05 and adult data therefore not different from adolescent data.

Available relevant data of study by Hall et al. (2024). Adult data only.

| Assessment or measurement | Placebo | THC | CBD+THC |
|---|---|---|---|
| Dose | - | 0.107 mg/kg | 0.320 mg/kg+0.107 mg/kg |
| CBD:THC ratio | - | 0:1 | 3:1 |
| Attentional bias - 200 ms presentation time - mean (SD) | -12.27* (23.39) | 1.21 (28.42) | −1.90 (27.99) |
| Attentional bias - 200 ms presentation time - median | −12.78 | 1.20 | -3.02 |
| Attentional bias - 200 ms presentation time - min-max | -65.90, 40.88 | -74.98, 46.57 | -44.97, 55.94 |

| Assessment or measurement | Placebo | THC | CBD+THC |
|---|---|---|---|
| Attentional bias - 500 ms presentation time -mean (SD) | −3.32 (36.17) | −17.47* (41.45) | 0.32 (20.44) |
| Attentional bias - 500 ms presentation time - median | −1.53 | −18.39 | 1.14 |
| Attentional bias - 500 ms presentation time - min-max | -81.80, 62.17 | -96.63, 57.36 | -32.89, 39.54 |

* One sample t-test significance for presence of attentional bias in sample $p<0.05$

Available relevant data of study by Hall et al. (2024). Combined adolescent and adult data.

| Assessment or measurement | Placebo | THC | CBD+THC |
|---|---|---|---|
| Dose | - | 0.107 mg/kg | 0.320 mg/kg+0.107 mg/kg |
| CBD:THC ratio | - | 0:1 | 3:1 |
| Attentional bias - 200 ms presentation time - MD | 11.724 | 15.436 | -3.712 |
| Attentional bias - 500 ms presentation time - MD | - | - | - |

Available relevant p-values for study by Hall et al. (2024). P-values were not reported for adult-only data and only available for combined adolescent and adult data.

| Assessment or measurement | Adolescents vs. adults (age*Drug) | THC vs. Placebo | CBD+THC vs. placebo | CBD+THC vs. THC |
|---|---|---|---|---|
| Attentional bias - 200 ms presentation time | ns. (p=0.402) | ns. (p=0.115) | p=0.040 | ns. (p=1) |
| Attentional bias - 500 ms presentation time | ns. (p=0.658) | ns. | ns. | ns. |

Combined adolescent and adult analyses assumed valid for adults-only interpretation when age*drug $p>0.05$ and adult data therefore not different from adolescent data.

Available relevant data of study by Oliver et al. (2024)

| Assessment or measurement | THC | CBD+THC | CBD+THC | CBD+THC |
|---|---|---|---|---|
| Dose | 10 mg | 10 mg + 10 mg | 20 mg + 10 mg | 30 mg + 10 mg |
| CBD:THC ratio | 0:1 | 1:1 | 2:1 | 3:1 |
| | Mean difference (95CIs) THC vs. baseline | EMM difference (95%CIs) CBD+THC (1:1) vs. THC | EMM difference (95%CIs) CBD+THC (2:1) vs. THC | EMM difference (95%CIs) CBD+THC (3:1) vs. THC |
| Attentional bias to cannabis (all trials) | 12.2 (1.20, 23.3) | 1.657 (-10.777, 14.092) | -1.991 (-14.344, 10.363) | 2.327 (-10.192, 14.846) |
| Attentional bias to cannabis (short duration) | 15.1 (−3.2, 33.4) | 14.541 (-1.804, 30.886) | 10.170 (-6.077, 26.417) | 11.297 (-5.150, 27.744) |
| Attentional bias to cannabis (long duration) | 9.8 (−7.0, 26.6) | 0.213 (-16.220, 16.645) | 5.113 (-11.214, 21.440) | 6.237 (-10.305, 22.779) |
| Attentional bias to food (all trials) | 6.3 (−5.4, 18.0) | -1.203 (-14.547, 12.141) | -1.079 (-14.340, 12.181) | 1.247 (-12.183, 14.677) |
| Attentional bias to food (short duration) | 11.3 (−3.0, 25.7) | 8.876 (-6.187, 23.938) | 12.362 (-2.605, 27.329) | 2.043 (-13.120, 17.205) |
| Attentional bias to food (long duration) | 0.3 (−11.7, 12.3) | -0.805 (-15.293, 13.683) | 2.623 (-11.780, 17.026) | 0.414 (-14.162, 14.989) |
| Picture rating cannabis | 0.3 (−0.1, 0.7) | 0.330 (0.041, 0.620) | 0.197 (-0.093, 0.486) | 0.137 (-0.153, 0.426) |
| Picture rating food | 0.3 (−0.02, 0.7) | 0.214 (-0.134, 0.562) | 0.126 (-0.221, 0.474) | -0.032 (-0.380, 0.315) |

Available relevant p-values for study by Oliver et al. (2024)

| Assessment or measurement | THC vs. baseline | CBD+THC (1:1) vs. THC | CBD+THC (2:1) vs. THC | CBD+THC (3:1) vs. THC |
|---|---|---|---|---|
| Attentional bias to cannabis (all trials) | p=0.03 | ns. (p=0.993) | ns. (p=0.988) | ns. (p=0.982) |
| Attentional bias to cannabis (short duration) | ns. (p=0.10) | ns. (p=0.282) | ns. (p=0.590) | ns. (p=0.512) |
| Attentional bias to cannabis (long duration) | ns. (p=0.25) | ns. (p=1.000) | ns. (p=0.922) | ns. (p=0.872) |
| Attentional bias to food (all trials) | ns. (p=0.29) | ns. (p=0.998) | ns. (p=0.998) | ns. (p=0.998) |
| Attentional bias to food (short duration) | ns. (p=0.12) | ns. (p=0.636) | ns. (p=0.347) | ns. (p=0.993) |
| Attentional bias to food (long duration) | ns. (p=0.96) | ns. (p=0.999) | ns. (p=0.983) | ns. (p=1.000) |
| Picture rating cannabis | ns. (p= 0.12) | ns. (p=0.104) | ns. (p=0.521) | ns. (p=0.778) |
| Picture rating food | ns. (p =0.06) | ns. (p=0.604) | ns. (p=0.884) | ns. (p=0.998) |