Medical Cannabis and Cannabinoids

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Abstracts

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Medical Cannabis and Cannabinoids

Abstracts

Abstracts of Oral Presentations

L-1

The Day Anandamide Almost Died and Other Endocannabinoid Stories

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My lecture will recount three forgotten moments in the history of endocannabinoid research. The first took place in 1996, when the newly discovered anandamide, the first endocannabinoid substance to be identified, came dangerously close to an untimely death. It may seem odd now, but back then, the idea that an unusually looking lipid molecule could transmit signals from one brain cell to another was viewed by many with a great deal of disbelief. So much that one bizarre circumstance almost consigned anandamide to the trash bin of science. The next story bears witness to the difficulties early researchers experienced in identifying the biochemical mechanisms through which anandamide is produced. Some of those difficulties are still with us today and await to be resolved. The last part of the lecture will describe the discovery of the second endocannabinoid, 2-arachidonoylglycerol, which until then had been considered a rather mundane intermediate in lipid metabolism but turned out to be one of the most pervasive modulatory transmitters in the mammalian brain. The lecture will mostly rely on published articles, lab notebooks, and personal correspondence and its main objective is to show that each of the events recounted was an important juncture in the progress of endocannabinoid studies, which is worth remembering along with its many protagonists and learned lessons. It is also my hope that the lecture will help the audience to acquire a deeper understanding of the endocannabinoid system, which will allow them to bring into focus the many open questions that need to be addressed by future research. **Keywords:** Endocannabinoid, anandamide, 2-arachidonoylglycerol.

L-2

Endocannabinoidome Signaling: From Gut to Brain and Across Different Kingdoms, and Intersections with Plant Cannabinoids

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The endocannabinoid (eCB) system is a complex signaling network discovered in mammals during the 1980s-90s when investigating the mechanism of action of the psychotropic cannabis component, Δ9-tetrahydrocannabinol (THC). It conventionally revolves around two arachidonic acid-derived mediators, i.e. *N*-arachidonoyl-ethanolamine (anandamide) and 2-arachidonoylglycerol (2-AG); their main receptors, i.e. the cannabinoid receptors of type 1 (CB1) and type 2 (CB2), and the transient receptor potential vanilloid-1 (TRPV1) channels; and the enzymes responsible for their biosynthesis and degradation. However, drawing on these discoveries, numerous other eCB-like signaling lipids have been unveiled in the last 25 years, together with their receptors and metabolic enzymes, which are often in common with the eCBs. Some years ago, I have defined this wider, and more complex, signaling network as the endocannabinoidome (eCBome). I will discuss the pharmacological complexity of the mammalian eCBome, highlighting its versatility and redundancy and how it serves as a better physiological substrate for non-THC cannabinoids than the «simple» eCB system. I will also describe the importance of other «eCBomes» in non-mammalian forms of life that populate the external and internal environments of mammals, with particular emphasis on those found in bacteria that colonize the gastrointestinal system. The emerging eCBome-mediated cross-talk between gut microbiota and their hosts is perhaps only the best known example of how this signaling system is used in inter-kingdom communication, the understanding of which is crucial to develop new therapeutic strategies in a more global context, such as that proposed by the One Health policy of the WHO.

L-3

Cannabinoid and Stress – Mechanistic Aspects

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Introduction: The endocannabinoid system has been shown to be involved in various aspects of stress coping. In the light of highly increased stress load in societies during recent time and the subsequent increase in mental health impacts, the understanding of how

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and under which circumstances endocannabinoid signaling is beneficial as a body's protective mechanism is highly relevant. The pharmacological modulation of the endocannabinoid anandamide seems to be particularly a promising therapeutic strategy. Using genetic models in the manipulation of endocannabinoid signaling in mouse may contribute to a deeper understanding of the complexity of the endocannabinoid signaling in stress coping and anxiety and may uncover insights into the beneficial as well as non-favorable effects of this signaling system. **Methods:** Several mutant mouse lines with impaired synthesis or degradation of anandamide, and impaired or enhanced CB1 receptor function were generated and investigated in a broad spectrum of behavioral assays, assessing stress coping, anxiety, explorative behavior and learning and memory. Mice were challenged by chronic social defeat stress or underwent fear conditioning and extinction paradigms. **Results:** The deficits of anandamide synthesis rather coherently led to increased anxiety behavior, independent of the time point of genetic deletion and stress load. However, the manipulation of anandamide degradation led to phenotypes divergent in some cases from the general notion that enhancing the anandamide tone to be mostly beneficial regarding anxiety-like behavior. Furthermore, increased CB1 receptor signaling was shown to be particularly beneficial in alleviating stress-induced reduction social interaction. **Conclusions:** The genetic impairment of anandamide degradation, leading to increased levels of anandamide and other acylamides, can evoke divergent effects, depending on time point of intervention as well as on the situational contexts, while inhibiting anandamide synthesis does not show this sensitivity of time and context.

L-4

50 Years of Cannabis Phytochemistry and Analytics

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Introduction: The cannabis research program at the University of Mississippi (UM) started in 1968, just 4 years from the discovery of the chemical structure Δ9-THC in 1964, which stimulated interest in cannabis research. The project progressed from the production of raw biomass to a full program producing different plant chemovars, extracts, standard cannabinoids for the research community and to the GMP manufacturing of different products for clinical trials. This presentation will elaborate on the history of this longest continually funded research project supported by NIH, topping 55 years now and the scientific accomplishments in the areas of phytochemistry and analytics as well as product development. **Aims:** It is the objective of this presentation to show the progress in the chemistry and analytical methods developed for cannabis and cannabis derived products over the span of 50+ years. **Methods:** The presentation will elaborate on the different methods used to determine the chemical structures of different chemical classes of cannabinoids and non-cannabinoids and the contributions made by the UM group in that area. Further, many new analytical methods were developed by UM scientists including GC/FID, GC/MS, HPLC, LC/MS/MS and others for cannabinoids and non-cannabinoid constituents. **Results:** The program discovered and determined the chemical structures of more cannabis constituents in the last few years than any other group, mainly cannabinoids and non-cannabinoid phenols and alkaloids. Analytically speaking, new methods were developed in all areas of methods development. **Conclusions:** The cannabis research program at UM has provided an important service to the cannabis research community, not only in providing drug supply, but also in the discovery of several new constituents and development of several analytical methods using a variety of techniques. **Keywords:** Cannabis research, University of Mississippi, cannabinoids, analytical methods, cannabis constituents. **Acknowledgements:** Supported by the National Institute on Drug Abuse, NIH, contract # 75N95023D00010.

L-5

Personalized Cannabis Medicines – What is the Evidence?

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Introduction: Cannabis-based medicinal products (CBMPs) have emerged as a promising option as an adjuvant for managing symptoms related to various medical conditions, including chronic pain, epilepsy, cancer and multiple sclerosis. However, the variability in inter-individual responses to cannabinoids underscores the wish for more personalized approaches. Despite such increasing interest, the evidence supporting personalized CBMPs remains fragmented and inconclusive. **Aims:** This presentation aims to summarize the current state of real-world evidence (RWE) on personalized CBMPs, focusing on their efficacy, safety, and clinical application. Additionally, it seeks to identify gaps in the existing literature and to propose future research directions. **Methods:** A non-systematic review of existing literature was conducted using databases including PubMed, Scopus, and Web of Science. Studies were selected based on their relevance to personalized CBMPs, focusing on observational studies using CBMPs varying in cannabinoid composition, as well as cohorts of patients with different clinical indications, ages and gender. Data extraction focused on patient outcomes, genetic factors, and dosing strategies. **Results:** The field of personalized CBMPs remains largely unexplored due to the intrinsic limitations of their prescription and the lack of solid evidence to support product selection. **Conclusions:** While existing RWE may support the potential of personalized CBMPs, significant gaps in high-quality, targeted research remain. Standardized analysis focusing on pharmacogenomics, dosing algorithms, and long-term safety are essential to advance personalized cannabis-based medicine. **Keywords:** Cannabis-based medicinal products, personalization, cannabinoids, pharmacogenomics, therapeutic outcomes. **Acknowledgements:** The authors thank the research teams and collaborators who contributed to the systematic review. The author is an employee of Khiron Europe, a distributor of CBMPs in Germany, Switzerland and the UK.

L-6

Sites and Mechanisms Underlying Cannabinoid-Induced Antinociception

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A large body of evidence indicates that endocannabinoids, phytocannabinoids, and synthetic cannabinoid receptor agonists are antinociceptive in animal models of pain-related conditions (e.g. acute, inflammatory, neuropathic pain). The endocannabinoid system (ECS), comprising the cannabinoid$_1$ receptor (CB1R) and cannabinoid$_2$ receptor (CB2R), endogenous cannabinoid ligands (endocannabinoids), and metabolizing enzymes, is present throughout the pain pathways. CB1R and CB2R located at peripheral, spinal, or supraspinal sites are important targets mediating the antinociceptive effects of cannabinoids and ECS modulators. Non-CB1R/non- CB2R targets of cannabinoids including TRPV1, GPR55, and PPARs also play an important role. The mechanisms underlying the antinociceptive effects of cannabinoids likely include inhibition of presynaptic neurotransmitter and neuropeptide release, modulation of postsynaptic neuronal excitability, activation of the descending inhibitory pain pathway, and reductions in neuroimmune and neuroinflammatory signaling. Our work has demonstrated a key role for the ECS in the effects of stress, fear and negative affect on pain-related behaviour in rodents, with supraspinal sites of action including the periaqueductal grey, amygdala and prefrontal cortex. Our work in both a rat model of low back pain and humans with low back pain indicates that the ECS may be a viable therapeutic and/or diagnostic target in this pain condition. Our recent data also provide evidence for sex dimorphism in the antinocieptive effects of ECS modulators. Potential strategies to dissociate the psychoactive effects of cannabinoids from their analgesic effects include peripherally restricted CB1R agonists, CB2R agonists, inhibitors of endocannabinoid catabolism, transport or uptake, and modulation of other non-CB1R/non- CB2R targets of cannabinoids. Evidence from clinical research in human participants lags behind that from preclinical studies but suggests that cannabinoids likely modulate the cognitive-affective component of pain. High quality clinical trials with cannabinoids and ECS modulators that show promise preclinically, but which have not yet been assessed in human participants are warranted, along with study of their sites and mechanisms of action.
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L-7

Sites and Mechanisms Underlying Cannabinoid-Induced Antinociception

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Chronic primary pain is chronic pain in one or more anatomical regions characterized by significant emotional distress and/or functional disability. Pathophysiologically, a dysfunction of the cortico-mesolimbic connectome is of great importance, with overlapping signals in the central nociceptive and stress systems, which – as preclinical and some clinical data suggest – are also controlled by the endocannabinoid system.

Experimental studies have shown that the more the cortico-mesolimbic connectivity is dysregulated, the greater the pain reduction provided by delta-9-tetrahydrocannabinol (THC). Qualitative studies of chronic pain patients who benefit from cannabis-based medicines (CBMs) have shown that it is not just pain relief that is the main effect, but a more holistic effect that includes, in particular, improved pain coping. Large observational studies also showed pleiotropic effects of CBMs with positive effects on pain intensity, sleep problems, depression, anxiety and reduction of opioids. Systematic reviews and meta-analyses (SRMAs) of randomized controlled trials (RCTs) showed a heterogeneous picture, which is why only very low to moderate evidence for the efficacy of CBMs in chronic pain can be determined at the level of external evidence. Large RCTs on the use of CBMs for chronic non-specific low back pain are underway. Their results are eagerly awaited. In summary, based on all available information in the sense of evidence-based medicine (external evidence, experience and preferences of physicians and patients), a pragmatic approach to the use of CBMs makes sense for chronic pain patients in whom standard procedures have not led to success.

Keywords: Cannabis-based medicines, chronic pain, central sensitization, chronic stress, evidence-based medicine.

L-8

Cannabinoids for Neurodegeneration - Fact or Fiction?

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The two major goals in neurodegenerative disorders such as Alzheimers disease, Parkinson Disease and Amyotrophic Lateral Sclerosis are slowing or halting disease progression and maintaining quality of life.

Basic research has revealed a huge potential for cannabinoid-based medications since the various cannabinoids interact with a plethora of pathways. With respect to modifying the disease course basic research has revealed profound neuroprotective effects across various neurodegenerative diseases but clinical trials are lagging behind the basic science. On the other hand, several clinical trials could show significant treatment effect on symptoms such as spasticity and cramps.

The presentation will review current knowledge of the endocannabinoid system in neurodegenerative diseases, neuroprotective mechanisms and symptomatic treatment effects. In addition, the challenges of performing clinical trials with cannabinoids will be highlighted.

L-9

CBMs in Psychiatric and Substance Use Disorders

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The endocannabinoid system represents a promising novel target for the treatment of psychiatric and substance use disorders. It is the most important neuromodulatory system in the brain and may induce beneficial effects by influencing the activity of specific neurotransmitter systems, particularly glutamate, GABA, dopamine and serotonin. In the last two decades, numerous publications of case reports, case series, observational studies and randomized controlled trials have reported on the efficacy and safety of medicinal cannabis and its isolated constituents in various psychiatric conditions. THC-containing cannabis preparations appear to be efficacious in the treatment of neurodevelopmental disorders, including ADHD and autism spectrum disorder. On the other hand, pure CBD seems to dose-dependently reduce social anxiety and PTSD symptoms and to improve sleep in chronic insomnia, whereas the effects on positive and negative symptoms of schizophrenia were mixed but mainly positive. Regarding addictive behaviors, both THC and CBD as well as the cannabis extract nabiximols have been found to improve distinct aspects of cannabis use disorders, such as cannabis use, craving and withdrawal symptoms. More recently, CBG, a minor phytocannabinoid and precursor to many other cannabinoids, has been demonstrated to reduce stress and anxiety and to improve cognition. Despite the variety of studies reporting beneficial effects of cannabis-based medicines, however, it is currently still premature to recommend them in psychiatric and substance use disorders due to the limited evidence. More controlled studies and clinical trials with greater sample sizes which also consider the long-term effects of medicinal cannabinoids are required to elucidate their therapeutic potential in psychiatry and addiction medicine. **Keywords:** Cannabis, THC, CBD, psychiatric disorders, substance use disorders.

L-10

Cannabinoid-based Therapies for Treating Metabolic Diseases

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Metabolic disorders, including obesity, type 2 diabetes, dyslipidemia, and metabolic dysfunction-associated steatotic liver disease (MASLD), represent significant global health challenges arising from the interplay of genetic predisposition, lifestyle factors such as diet and physical activity, and environmental influences. These disorders are marked by chronic disruptions in metabolic homeostasis, driving systemic inflammation, insulin resistance, and altered lipid metabolism. These pathophysiological changes substantially elevate the risk of cardiovascular diseases, cancer, and other comorbidities, contributing to increased morbidity and mortality, particularly in Westernized societies characterized by sedentary lifestyles and calorie-rich diets.

The endocannabinoid system (ECS) has emerged as a central regulator of energy balance, appetite, and metabolism. Dysregulation of the ECS, particularly through the overactivation of the cannabinoid-type 1 receptor (CB_1R), plays a significant role in the development and progression of metabolic disorders. Cannabis and its psychoactive component, Δ^9-tetrahydrocannabinol (THC), are well-recognized for their ability to enhance appetite («munchies») via CB_1R activation, highlighting the receptor's critical role in metabolic regulation.

This presentation will highlight innovative therapeutic strategies targeting the ECS to address metabolic syndrome and its associated abnormalities. These include leveraging the potential of plant-derived cannabinoids, such as the non-psychoactive compounds cannabidiol (CBD) and cannabigerol (CBG), which demonstrate promising metabolic effects. Additionally, advancements in synthetic cannabinoid pharmaceuticals, including a stable and therapeutically optimized derivative of cannabidiolic acid, are paving the way for enhanced therapeutic efficacy. Another approach involves peripherally restricted CB_1R blockers, which are designed to avoid central side effects while maintaining metabolic benefits.

Collectively, these diverse strategies employ distinct molecular mechanisms yet converge in their ability to reverse obesity and metabolic abnormalities. This talk will explore preclinical and translational advancements, emphasizing the promise of cannabinoid-based therapies in addressing the global burden of metabolic diseases.

L-11

The Value of Real-World Evidence in Cannabis Therapies

A.K. Schlag[1]

[1]Drug Science, Imperial College London, Yetminster, UK

Introduction: Randomised controlled trials (RCTs) have long been considered the gold standard of medical evidence. In relation to cannabis based medicinal products (CBMPs), this focus on RCTs has led to restrictive guidelines in the UK, limiting patient access. There is general agreement that RCT evidence in relation to CBPMs is insufficient at present for many conditions. A major problem is that RCTs do not lend themselves well to the study of whole plant medicines. One solution to this challenge is the use of real-world evidence (RWE) with patient reported outcomes (PROs) to widen the evidence base. Our presentation outlines the value of this approach which involves the study of interventions and patients longitudinally under medical care. **Aims:** Project Twenty21 (T21) documented patterns of prescribed cannabis use and health related outcomes, including general health and quality of life as well as condition-specific symptoms in a large cohort of individuals accessing CBMPs through private health care in the

United Kingdom (UK). We also examined changes in the use of prescribed opioids among chronic pain patients receiving CBMPs. These issues are examined using data from T21. **Methods:** Launched in August 2020, T21 developed RWE on the effectiveness and safety of medical cannabis. T21 was a multi-centre, prospective, observational patient registry of RWD that includes data from patients receiving medical cannabis for a broad variety of conditions. **Results:** By 1st July, 2024 data from 4500+ individuals had been contributed to T21. We summarise patients' health outcomes over this period, highlighting how treatment with CBMPs is associated with substantial improvements in various specific conditions, comorbidities, as well as in patients' quality of life generally. **Conclusions:** In line with other international RWE studies, T21 clearly shows the benefits of CBMPs in treating a broad variety of conditions. RWE data increasingly highlights the positive impact medical cannabis can have on patients' lives. Indeed, CBMPs may have a particular role in addressing unmet clinical need, such as in relation to comorbidities. Excluding comorbid or older patients in RCTs may risk recruiting an unrepresentative sample and exclude patients who would most benefit. **Keywords:** Cannabis-based medical products (CBMPs), real-world evidence (RWE), patient reported outcomes (PROs), Project Twenty21 (T21). **Acknowledgements:** We thank all T21 patients who provided their data to develop the scientific evidence based on medical cannabis. We would like to express gratitude to our partners whose generosity enabled T21 patients to receive their CBMPs at a reduced rate: Somai Pharmaceuticals, Blackpoint Biotech, Ethypharm, 4CLabs, Cellen Biotech LtD., JMCC Group, Khiron Life Sciences Corp., and Lyphe Group.

References:

[1] Schlag AK, Nutt DJ, Lynskey M. Using real world evidence to optimize care: the case of medical cannabis. Expert Rev Pharmacoecon Outcomes Res 2024; Apr;24(4): 463-465. doi: 10.1080/14737167.2024.2322005. Epub 2024 Feb 23. PMID: 38392352.

[2] Schlag AK, Zafar RR, Lynskey MT, Athanasiou-Fragkouli A, Phillips LD, Nutt DJ. The value of real world evidence: The case of medical cannabis. Front Psychiatry 2022; Nov 3;13:1027159. doi: 10.3389/fpsyt.2022.1027159. PMID: 36405915; PMCID: PMC9669276.

[3] Lynskey MT, Schlag AK, Athanasiou-Fragkouli A, Badcock D, Nutt DJ. Characteristics of and 3-month health outcomes for people seeking treatment with prescribed cannabis: Real-world evidence from Project Twenty21. Drug Science, Policy and Law 2023; 9. doi:10.1177/20503245231167373

L-12

The Use of Tetrahydrocannabinol in Palliative Cancer Patients

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Introduction: Palliative cancer patients are suffering from multimorbidities and various neuro-psychiatric symptoms, with total pain as maximal «syndromal entourage». Moreover, pain is often insufficiently treated, and polypharmacotherapy has the risk of severe side effects and drug interactions. **Aim:** This lecture discusses the chances of medical cannabis (MC) for reduction of syndromal entourage, for the improvement of pain and for the reduction of neuro-psychiatric polypharmacological treatment. **Methods:** Review of international publication accessible in PubMed; experiences from MC prescribing doctors; insights from the Belcanto-Trial, a RCT with the author as initiator and representative of the sponsor. **Results:** As with all indications, the meta-analyses show contradictory results. A recent umbrella-review (Solmi et al. 2023) provides evidence for therapeutic MC effects in cancer patients. Observational studies demonstrate MC effects in palliative care, e.g. for neuropathic pain, vomiting, quality of life, insomnia and repeatedly, reduction of opioids and neuro-psychiatric comedication. Observational studies of the authors home university demonstrate that MC are well tolerated in palliative cancer patients. Older age does not argue against MC. **Conclusions:** MC might effective against the syndromale entourage of total pain, as it occurs in palliative cancer patients, i.e. anxiety, depression, insomnia, pain, loss of appetite, muscle spasms and/or emesis. **Keywords:** Medical cannabis, pain, quality of life, comedication.

L-13

Cannabis-based Medicines in Sleep Disorders

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Introduction: Sleep disorders relate to the patient's dissatisfaction regarding quality, timing, and amount of sleep resulting in daytime distress and impairment in functioning. They often co-occur with other medical conditions and are often accompanied by depression, anxiety, and cognitive changes. Insomnia is the most common sleep disorder and involves problems getting to sleep or staying asleep. Other sleep disorders include obstructive sleep apnea (OSA), parasomnias, narcolepsy, and restless leg syndrome (RLS). Treatment of sleep problems involves sleep hygiene, relaxation techniques, behavioral therapy such as cognitive behavior therapy, and sleep medications including antihistamines, antidepressants, anti-psychotics, melatonin as well as compounds that can become habit-forming such as benzodiazepines and Z-drugs. **Aims:** To give a comprehensive overview about current clinical data on the effectiveness of cannabis-based treatment of sleep disorders. **Methods:** A literature search were conducted in PubMed. **Results:** From several large surveys it is well known for many years that a substantial number of individuals uses cannabis to (self-) treat problems of initiating and maintaining sleep. According to a systematic review published in 2022 cannabis-based medications improve impaired sleep in patients with chronic pain, but the magnitude of benefit is likely small. In insomnia, 10 controlled studies (RCT) have been performed mainly in small samples using different cannabinoids (delta-9-tetrahydrocannabinol, THC; cannabidiol, CBD; cannabinol, CBN; cannabigerol, CBG; cannabichromene, CBC; or extracts with different combinations of cannabinoids) at different doses. While there is limited evidence that THC and CBN improves short-term subjective sleep quality, low-dose CBD was ineffective. In OSA, 2 RCTs used THC and provided insufficient evidence for efficacy. In RLS, in one small RCT, CBD was

not effective. **Conclusions:** Although the number of RCTs is increasing, the database is still weak, and evidence remains insufficient to support efficacy of cannabinoids in sleep disorders. This is also related to the fact that in recent RCTs several different cannabinoids at different doses have been used. While in recent RCTs mainly efficacy of CBD, CBD-dominant extracts, and CBN has been investigated, in contrast from real-world data it is suggested that THC dominant products may improve sleep disorders.
Keywords: Sleep, insomnia, sleep apnoea, chronic pain, restless legs syndrome.

L-14

Medical Cannabis for Behavioral Symptoms in Patients with Severe Dementia: The MedCanDem Study

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Introduction: The use of medical cannabis is gaining attention as a therapeutic option in geriatrics. The elderly population represents a vulnerable demographic group with significant unmet medical needs, often linked to chronic comorbidities for which traditional pharmacological management may be insufficient or associated with substantial side effects. Behavioral disturbance in dementia is one of these unmet needs. Medical cannabis may be a potential therapeutic option; however, scientific evidence regarding its use in elderly patients remains limited, with critical questions about optimal dosages, interactions, and safety still unanswered. **Aims:** To address these gaps, the MedCanDem study [1] was designed to provide robust evidence on the efficacy and safety of medical cannabis in elderly patients with dementia experiencing behavioral disturbances. **Methods:** The MedCanDem study is a randomized, double-blind, placebo-controlled AB/BA crossover trial. Patients with severe dementia, pain, and behavioral disturbances residing in 5 specialized long-term care facilities in Geneva, Switzerland, were included. Consent was obtained from families and relatives. Participants were randomized 1:1 to receive either the intervention (THC-CBD 1:2 oil extract) or placebo (hemp seed oil) for 8 weeks, followed by a one-week washout and a crossover for another 8 weeks. Daily safety monitoring and a strict dosage titration protocol were implemented throughout the study period. **Results:** The trial was conducted from September 2023 to November 2024. The study was proposed to 30 relatives, all of whom provided consent; only one relative withdrew consent during the study. A total of 27 patients met the inclusion criteria and were enrolled, with 19 completing both study periods. Preliminary findings indicate the treatment's safety, with 4 patients experiencing serious adverse events, none related to the study treatment. Two patients died due to underlying frailty and medical conditions unrelated to cannabis treatment. The extensive database collected is currently under analysis (as of February 2025). **Conclusions:** Conducted in a «real world setting» the MedCanDem study demonstrated that clinical trials with medical cannabis within an elderly population with severe dementia can be executed efficiently. Our study may help standardize treatment protocols and evaluate the broader applicability of medical cannabis in geriatric care, notably on behavioral symptoms and chronic pain.
Acknowledgements: We would like to express our sincere gratitude to the staff at the participating long-term care facilities for their incredible support throughout the study. A special thought goes to Christian De Saussure. Without his invaluable contributions, none of this would have been possible.

Reference:

[1] Bianchi F, Pautex S, Wampfler J, Curtin F, Daali Y, Desmeules JA, Broers B. Medical cannabinoids for painful symptoms in patients with severe dementia: a randomized, double-blind cross-over placebo-controlled trial protocol. Front Pain Res (Lausanne) 2023; (May 24) 4: 1108832. doi: 10.3389/fpain.2023.1108832. PMID: 37293434; PMCID: PMC10244760.

L-15

Cannabis in Pain Treatment: The Challenge between Science and Clinical Evidence

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The endocannabinoid system is ubiquitous in the animal kingdom. Cannabinoid receptors and ligands can be found in the peripheral and central nervous system, where the endocannabinoid neuromodulatory system is involved in multiple physiological functions, such as anti-nociception and pain modulation.

With respect to the multi-dimensional character of pain, the endocannabinoid system is ideally located in all peripheral and central nervous system structures that are important for the processing and modulation of somato-sensory, affective-motivational and cognitive aspects of pain. However, in contrast to the striking evidence of cannabinoid effects on pain from animal studies, the significance of therapeutic benefit in clinical studies remains limited. There are many reports of observational studies, anecdotal reports, and even systematic reviews, but very few randomized clinical trials. Systematic reviews of available randomised controlled trials have stated low-quality evidence for various chronic pain conditions. Thus, in clinical reality, the treatment of chronic pain with medical cannabis is still controversial [1].

Recently, the development of a high-end cannabinoid-based pharmacological product is aiming to convert discoveries in the laboratory into better treatments for patients. One such new compound for the treatment of chronic pain is AP707 with the API Adezunap that was developed to provide a product with increased bioavailability, and to overcome limited therapeutic efficacy. AP707 is an aqueous nano dispersion of a THC-focused Cannabis flos genetic with a particle size of < 0.3 µm and a defined chemical fingerprint. As an oromocusal spray for sublingual application, dosing of AP707 is simple, accurate, and reproducible, in contrast

to the combusted use of smoked Cannabis for medical purposes. A phase I trial to determine the pharmacokinetics, psychotropic effects, and safety profile of the novel nanoparticle-based cannabinoid spray for oromucosal delivery highlights a remarkable innovation in galenic technology and urges clinical studies further detailing the huge therapeutic potential of medical cannabis [2]. The currently conducted RCTs in back pain, post-surgical/post-operative pain, DPN and central pain will analyze the clinical efficacy on pain reduction, beneficial effects on quality of life and improved tolerability for patients.

In summary, the endocannabionoid system is an evolutionarily highly conserved group of neuromodulatory lipids, receptors, and anabolic and catabolic enzymes, that are a involved in a plethora of physiological and pathological processes. For this reason, cannabis has been used for centuries for medicinal purposes and the treatment of pain [3]. It is now the time to step-by-step translate basic scientific knowledge on cannabinoids into sound clinical evidence and routine medical practice.

References:

[1] Petzke F et al. Cannabis-Based Medicines and Medical Cannabis for Chronic Neuropathic Pain. Drugs 2022; 36(1): 31-44.
[2] Lorenzl S et al. A Phase I Trial to Determine the Pharmacokinetics, Psychotropic Effects, and Safety Profile of a Noveel Nanoparticle-Based Cannabinoid Spray for Oromucosal Delivery. Med Cannabis Cannabinoids 2022; Jan 18; 5(1): 9-19.
[3] Zieglgänsberger W et al. Chronic Pain and the Endocannabinoid System: Smart Lipids – A Novel Therapeutic Option. Med Cannabis Cannabinoids 2022; Mar 22; 5(1): 61-75.

L-16
Cannabinoid Drug-Drug Interactions

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Introduction: The recent increase in legalized recreational and medical cannabis combined with the availability of unregulated over-the-counter products (e.g., cannabidiol (CBD) oil, and delta-8-tetrahydrocannabinol (Δ^8-THC)) creates the potential for unintended health consequences [1]. Delta-9-tetrahydrocannabinol (Δ^9-THC) and cannabidiol (the most abundant cannabinoid) are metabolized by the same enzymes that are responsible for the metabolism of many prescription medications (CYP3A4, CYP2C9, CYP2C19). As a result, we predicted that there will be instances of drug-drug interactions with the potential for adverse outcomes – particularly for medications with a narrow therapeutic index. **Aims:** We conducted a systematic review to identify reports of documented cannabinoid interactions with prescription medications [2]. Moreover, we have developed a free online tool for highlighting potential drug-drug interactions between cannabis/cannabinoids and prescription medications [3]. **Results:** Our review identified 31 reports where cannabinoids altered pharmacokinetics and/or produced adverse events. These papers involved 16 different Narrow Therapeutic Index (NTI) medications, under six drug classes, involving 603 cannabis or cannabinoid users. Interactions with warfarin, valproate, tacrolimus, and sirolimus were the most common interactions and may pose the greatest risk to patients. Common adverse events included increased bleeding risk, complications with anesthesia, altered mental status, and gastrointestinal distress. Additionally, we identified 18 instances in which clinicians identified an unexpected serum level for the prescribed drug. The CANNabinoid Drug Interaction Review (CANN-DIR®; www.CANN-DIR.psu.edu) is a free, web-based platform that has been developed to identify potential drug-drug interactions where Δ^9-THC and/or CBD may affect the metabolism of another prescribed medication. CANN-DIR is based on US FDA-approved prescribing information for the prescription cannabinoids (dronabinol, nabilone, nabiximols, and prescription CBD) and for prescribing information for medications sharing similar metabolic enzymes. CANN-DIR provides a readily accessible review of cannabinoid drug-drug interaction information for both the patient and health care provider. Moreover, this tool is available in eleven languages and his been acccessed from 94 countries to date. **Conclusions:** Cannabinoid-associated drug-drug interactions are likely among prescription medications that engage common CYP450 systems. Our findings highlight the need for healthcare providers and patients/caregivers to openly communicate about cannabis/cannabinoid use to prevent unintended adverse events. To that end, we have developed the free online tool CANN-DIR® to highlight potential cannabinoid drug-drug interactions with prescription medications. **Keywords:** Cannabis, CBD, drug-drug interactions, pharmacokinetics, THC. **Acknowledgements:** We thank the many members of the Penn State Center for Cannabis and Natural Products Therapeutics (CCNPP) who contributed to this work.

References:

[1] Kocis PT and Vrana KE. Delta-9-tetrahydrocannabinol (Δ^9-THC) and cannabidiol (CBD) drug-drug interactions. Med Cannabis Cannabinoids 2020; July 7; 3: 61-73. PMID: 34676340
[2] Nachnani R et al. Systematic Review of the Drug-Drug Interactions of THC, CBD, and Cannabis. Front Pharmacol 2024; May 22; 15: 1282831. PMID: 38868665
[3] Kocis P et al. CANNabinoid Drug Interaction Review (CANN-DIR™) Med Cannabis Cannabinoids 2023; Jan 12; 6(1): 1-7. PMID: 36814686

L-17
Risks of Cannabis-based Medicine

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Introduction: The therapeutic use of cannabis and cannabinoids has exploded in recent years and includes a vast range of products, from prescription medications with demonstrated efficacy to hemp oils and vaping devices with no evidence of efficacy to date [1]. Although there is clear therapeutic potential of cannabis and cannabinoids for certain endpoints, there are also risks of daily use, including Cannabis Use Disorder (CUD). Patients using cannabis for therapeutic use have higher rates of CUD than those using

it for non-therapeutic reasons, and the mechanism for this is not well understood. **Aims:** This presentation will discuss how cannabis influences therapeutic outcomes, such as pain, within the context of measures relevant to CUD. **Methods:** Human laboratory studies provide placebo-controlled data to inform our understanding of the therapeutic and non-therapeutic effects of controlled administration of cannabis varying in the primary phytocannabinoids, Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD). These studies demonstrate the time course and behavioral effects of cannabis across a range of subjective and objective endpoints: positive subjective effects, self-administration, mood, sleep, food intake, cognitive performance, and pain outcomes. These studies also demonstrate the consequences of abrupt cessation of cannabis use on mood, sleep, and food intake. Specific issues to be discussed in this talk: (1) Tolerance: How and when tolerance develops following repeated cannabis administration varies as a function of the therapeutic and non-therapeutic endpoint tested, yet there is little understanding of how the effects of different cannabis chemovars change over time. (2) Abstinence: Anesthesiologists note that cannabis users have higher analgesic requirements than non-cannabis users, yet there is little controlled evidence on the magnitude or duration of altered pain sensitivity following abrupt cannabis cessation. **Results and Conclusions:** Given that pain is one of the primary reasons that cannabis is used therapeutically, it is essential to have a more comprehensive understanding of how therapeutic and non-therapeutic endpoints interact. Measures of abuse liability should be included in studies assessing therapeutic potential to best understand the risks/benefits for a particular patient population change with repeated administration of cannabis chemovars relative to inactive cannabis [2]. **Keywords:** Marijuana, medical cannabis, cannabidiol. **Acknowledgment:** National Institue of Health for supporting this research and supplying the study cannabis.

References:

[1] Haney M, Cooper ZD, VanLaanen H; Hindocha C, Triemstra JL. Studies of cannabinoid-based products in clinicalTrials.gov: A scoping review. JAMA Network Open (under review)
[2] Haney M. Perspectives on cannabis research: Barriers and recommendations. JAMA Psychiatry 2020; 77: 994-995.

L-18

Challenges and Opportunities of Cannabis e-Cigarettes (e-Joints)

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Beyond psychiatric outcomes, the major health hazard associated with non-medical cannabis use are related to smoking cannabis, mixing it with tobacco and concurrent tobacco smoking. Regulation opens the door to harm reduction strategies like counseling users to vape, vaporize, or eat cannabis instead of smoking it. Given that more than of cannabis users are also daily smokers in Switzerland, regulated sale in pharmacies can enable focused tobacco smoking cessation interventions. Since 2022, an amendment of the Narcotics Act enables researchers to perform pilot regulation trials. The purpose of the pilot trials is to provide a basis for evidence-based decision-making about subsequent amendments of the law.

We launched the Safer Cannabis in Pharmacies Trial (SCRIPT), which includes 1091 participants in 3 cities in Switzerland in 2022. In the SCRIPT RCT, the intervention group will be allowed to buy cannabis in pharmacies and receive harm reduction counseling (avoid mixing cannabis with tobacco, encourage lower THC/higher CBD cannabis, vaporizing, vaping, or eating cannabis). Those also smoking tobacco will be offered a dedicated smoking cessation counseling intervention including recommendations for alternate nicotine delivery systems. The control group will receive the same interventions after the 6-months follow-up visit. Both groups will join a cohort followed for up to 24 months. In preparation to the trial, we performed rigorous toxicological assessments of inhaled forms of cannabis ranging from smoked blossoms, with or without filter, vaporizers and e-joints. Our activities in testing the health effects of harm reduction strategies for cannabis and tobacco users provide a unique opportunity to estimate the health benefits associated with alternate delivery systems within the context of a randomized controlled trial.

L-19

MEMORY & Research within the Florida Medical Marijuana Consortium

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Introduction: The Consortium for Medical Marijuana Clinical Outcomes Research is funded by Florida legislation to generate evidence on the safety and effectiveness of medical uses of cannabis. Central to its research mission is the novel Medical Marijuana Outcomes Repository (MEMORY), which offers critical infrastructure for controlled clinical research. **Aims:** To introduce the Consortium, to introduce and describe MEMORY developed by the Consortium, and to illustrate its use for cannabis use surveillance and outcomes assessment. **Methods:** Using deterministic linkages, MEMORY combines patient-level cannabis dispensing data from the Medical Marijuana Use Registry, administrative billing records of Florida residents with Medicaid and/or Medicare coverage, and Florida vital records including birth, death and fetal death certificates. Surveillance-related analyses include algorithms developed to track daily doses of delta-9-tetrahydrocannabinol (THC) and persistence across patient groups, indications, dosage forms, and calendar time; and assess reports of adverse events by physicians who certify patients for medical marijuana use. **Results:** As of June 2024, MEMORY contains data for approximately 1.4 million medical marijuana users who have been linked to approximately 300,000 individuals in Medicaid, 125,000 individuals in

Medicare, 100,000 birth and 50,000 death records. Daily doses of THC exceed those observed in clinical trials across all age groups and indications, especially for inhaled dosage forms. Although permitted, utilization of medical marijuana by children is minimal and has decreased over time, while utilization by young adults is steadily increasing. Considering disease prevalences in the state, indications that are over-represented among users include PTSD, cancer, amyotrophic lateral sclerosis, Crohn's disease, multiple sclerosis or conditions with similar symptomatology, but not pain or epilepsy. Ongoing inferential analyses evaluate the effect of cannabis on the risk of traffic accidents and on opioid dosing among long-term opioid users. **Conclusions:** The Consortium provides infrastructure for medical marijuana use surveillance and observational research that can inform policy and clinical practice. **Keywords:** Marijuana safety, medical marijuana effectiveness, cannabis use repositories, cannabis surveillance. **Acknowledgments:** The Consortium receives funding from the state of Florida. MEMORY encompasses data provided by the Florida Department of Health, the Florida Agency for Healthcare Administration and the Centers for Medicare and Medicaid Services.

L-20

Spatial Mapping of Endocannabinoidome in Brain by MALDI-2 MS-Imaging

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Introduction: Endocannabinoids (eCBs) are endogenous lipid messengers that primarily bind cannabinoid receptors CB1/CB2 and together with the enzymes that regulate their biosynthesis and degradation define the endocannabinoid system. The eCB signaling system plays a key role in the central nervous system, resulting altered in most neurological disorders. The analysis of eCBs is challenging for their low concentration in biospecimens, and this is exacerbated in Mass Spectrometry Imaging (MSI) where low sensitivity and tissue dependent ion suppression obscure their spatial visualization. **Aims:** In this work we address this limitation by the application of laser-induced post-ionization (MALDI-2). **Methods and Results:** Herein we demonstrate that MALDI-2 boosts the detection of 2-arachidonylglycerol (2-AG) and N-acylethanolamines (AEA, PEA, OEA) with respect to MALDI, and that eCBs can be visualized in brain at endogenous concentration only by MALDI-2-MSI. Both root-mean-square (RMS) and deuterated internal standards (I.S.) normalization were evaluated, with I.S. normalization providing improved pixel to pixel variation and more uniform distribution in specific brain regions, especially for 2-AG and PEA. Furthermore, high lateral resolution up to 5-μm pixel size was evaluated, resulting in the detection of all eCBs and confirming the MALDI-2 potential even reducing the ablated tissue amount. Lastly the method was applied as proof of concept in a mouse model of mild traumatic brain injury demonstrating the ability to reveal valuable biological insights for neuropharmacology. **Keywords:** Mass spectrometry imaging, endocannabinoids, spatial distribution, MALDI-2, Alzheimer's disease. **Acknowledgements:** Ministero dell'Università e della Ricerca (MIUR) project PIR01_00032 BIO OPEN LAB BOL «CUP» J37E19000050007, project CIR01_00032 – BOL «BIO Open Lab - Rafforzamento del capitale umano», project «Pathogen Readiness Platform for CERIC ERIC upgrade» - PRP@CERIC CUP J97G22000400006, project National Center for Gene Therapy and Drugs based on RNA Technology CUP: D43C2200120000 and USAMRDC Peer Reviewed Alzheimer's Research Program Convergence Science Research Award Program Announcement (Funding Opportunity Announcement Number W81XWH-19-PRARP-CSRA), Award number: W81XWH1810000.

L-21

Cannabis and Opioid Interactions: Abuse Potential, Physiologic Effects and Safety Profile in Humans

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Introduction: Opioid misuse is a global epidemic, with an estimated 33 million people worldwide misusing opioids. Medical and recreational use of cannabis is also rapidly increasing. However, there are no controlled data available on the safety and abuse potential of supratherapeutic opioid-cannabinoid drug combinations (i.e., doses/routes that occur with misuse); data is also lacking on the effects of cannabis in those with opioid use disorder. **Aims:** To evaluate the effects of inhaled cannabis (0, 10, 30 mg), intranasal oxycodone (0, 15, 30 mg) and their combination on abuse liability, physiological effects and their safety profile in humans. **Methods:** Participants with mild to moderate opioid use disorder (but without physical dependence on opioids) and a history of cannabis use were enrolled into this within-subject, randomized, double-blind, placebo-controlled, inpatient study (n=9). During each session, an inhaled vaporized cannabis dose (0, 10, 30 mg THC) was administered 15 min prior to an intranasal oxycodone dose (0, 15, 30 mg). Participants received all dose combinations across 9 experimental sessions. Data were collected prior to (baseline) and in regular intervals for 6 h after dose administration. Primary outcomes include safety/physiologic outcomes (e.g., oxygen saturation, end tidal carbon dioxide concentration [$EtCO_2$]), respiration rate) and subjective measures of abuse potential (e.g., drug liking, feeling high, take drug again). **Results:** When administered separately, oxycodone and cannabis produced prototypical, dose-related effects; for example, dose-related increases in abuse-related subjective effects (e.g., drug liking, high) relative to placebo ($p < 0.05$). As displayed in Fig. 1, when active doses were administered in combination: (1) peak subjective ratings increased in magnitude and (2) the duration of effects were longer, relative to either drug alone (i.e., overall greater AUC with drug combination). Cannabis alone did not alter breathing outcomes and did not alter opioid-induced respiratory depression ($EtCO_2$; $p > 0.05$). **Conclusions:** Co-administration of supratherapeutic doses of cannabis and opioids increase

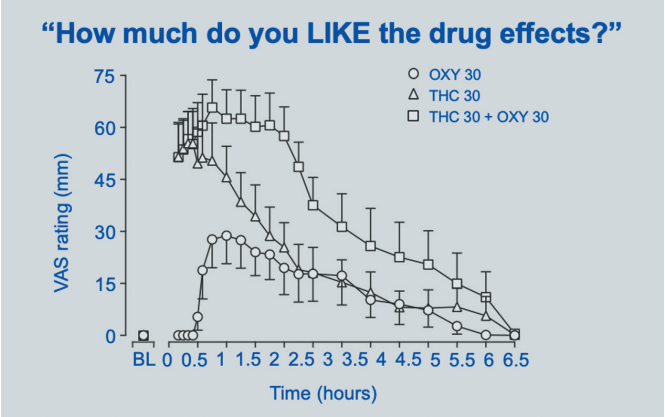

Figure 1.

abuse-related subjective effects, which is worrisome for those using these drugs together for either therapeutic or non-medical use. There was no evidence under these dose conditions of enhanced physiological risk (e.g., no worsening respiratory function), suggesting that it is a safe combination to explore for possible therapeutic effects. **Keywords:** Cannabis, opioids, drug interaction, abuse potential, human. **Acknowledgements:** Supported by grant from the National Institute on Drug Abuse (R01DA045700).

L-22

Cannabinoids and Cancer: the Impact of Cannabidiol on Chronic Myelogenous Leukaemia

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Introduction: An increasing number of studies have been carried out to assess the biological activities of *Cannabis sativa* L. extracts and cannabinoids, including the possible anticancer effects. Accordingly, there is considerable interest in cannabinoid-mediated inhibition of cancer cell proliferation, invasion and angiogenesis, as well as induction of apoptosis and autophagy. **Aims:** This study aimed to assess the antiproliferative activity of chemically characterized extracts from non-psychoactive *C. sativa* (hemp) and to disclose the possible mechanism/s of action of the main cannabinoids. **Methods:** Hemp extracts from different plant varieties were analysed by ultra high-performance liquid chromatography coupled with high-resolution mass spectrometry (UHPLC-HRMS), and the compounds were quantified using HPLC-UV [1]. The antiproliferative activity of the extracts was assessed *in vitro* against a panel of human cancer cell lines [1]. To shed light on the cannabidiol (CBD) apoptotic mechanism of action, a functional proteomic study based on «Drug Affinity Responsive Target Stability» (DARTS) was performed to identify its interactome in chronic myelogenous leukaemia (CML) K562 cells, which were the most sensitive ones to the treatment [2]. Finally, a lipidomic study was carried out to disclose the metabolic changes that occurred in the cellular lipid pattern of K562 cells following the treatment with CBD to determine significant alterations of the cell metabolism attributable to the induction of apoptosis. **Results:** A CBD-type hemp extract was able to inhibit cell proliferation in a dose-dependent way [1]. An increase of cytochrome c in the cytosol was determined together with activation of caspases 3 and 7 [1]. The results obtained using DARTS showed the ability of CBD to target simultaneously some potential protein partners, corroborating its well-known poly-pharmacology activity [2]. In human CML K562 cancer cells, the most fascinating protein partner was identified as the 116 kDa U5 small nuclear ribonucleoprotein element called EFTUD2, which fits with the spliceosome complex [2]. The binding mode of this oncogenic protein with CBD was clarified using MS-based and in silico analysis [2]. The comprehensive characterization of the changes in the lipid metabolism in K562 cancer cells treated with CBD unveiled several classes affected by the compound, including cardiolipins (CL), phosphatidylcholines (PC), phosphosphingolipids (SM) and triacylglycerols (TG). **Conclusions:** Even if further work is necessary to validate the results on different cell lines, the present research supports CBD as a possible candidate for future therapy of CML either alone or in association with other anticancer drugs. **Keywords:** *Cannabis sativa* L., cannabidiol, antiproliferative activity, leukaemia, omics.

Reference:

[1] Anceschi L et al. Chemical characterization of non-psychoactive *Cannabis sativa* L. extracts, in vitro antiproliferative activity and induction of apoptosis in chronic myelogenous leukaemia cancer cells. Phtyoter Res 2022; 36: 914-927.

L-23

A Cannabidiol Cocrystal (ART12.11) Tablet Has Comparable Pharmacokinetics to Epidiolex®

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Introduction: Cannabidiol (CBD) is useful in treating a range of conditions. For broader use, especially in adult populations, an oral solid formulation may be preferred. However, solid formulations have been limited by CBD's physical properties. Cocrystallisation is a pharmaceutical strategy to improve physicochemical properties of difficult active pharmaceutical ingredients (API) (Figure 1A). Artelo Biosciences have developed a patented cocrystal of CBD with the co-former tetramethylpyrazine (TMP; also called ligustrazine), designated ART12.11 (Figure 1B). Artelo previously reported that an unoptimised oral solution of ART12.11 has improved pharmacokinetic (PK) and pharmacodynamic properties compared to CBD in multiple species. **Aim:** To develop an optimised tablet of ART12.11. **Methods:** Prototype formulations were manufactured using common pharmaceutical techniques for compression tableting. The

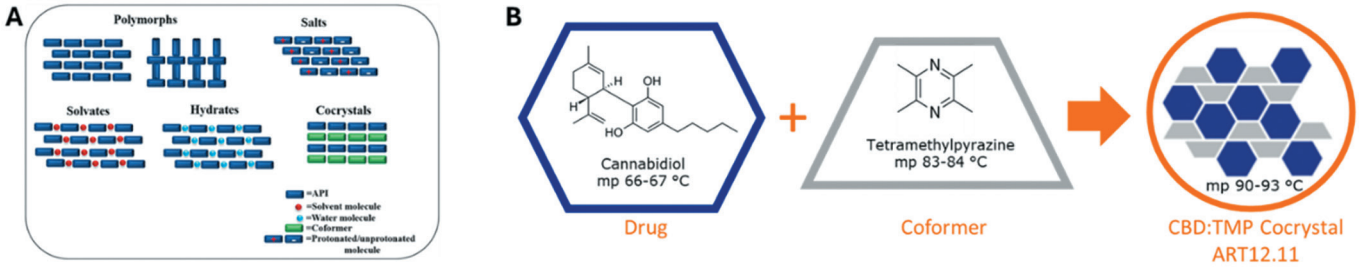

Figure 1. A: Pharmaceutical strategies for solid forms of API. B: ART12.11 is a cocrystal of CBD and TMP

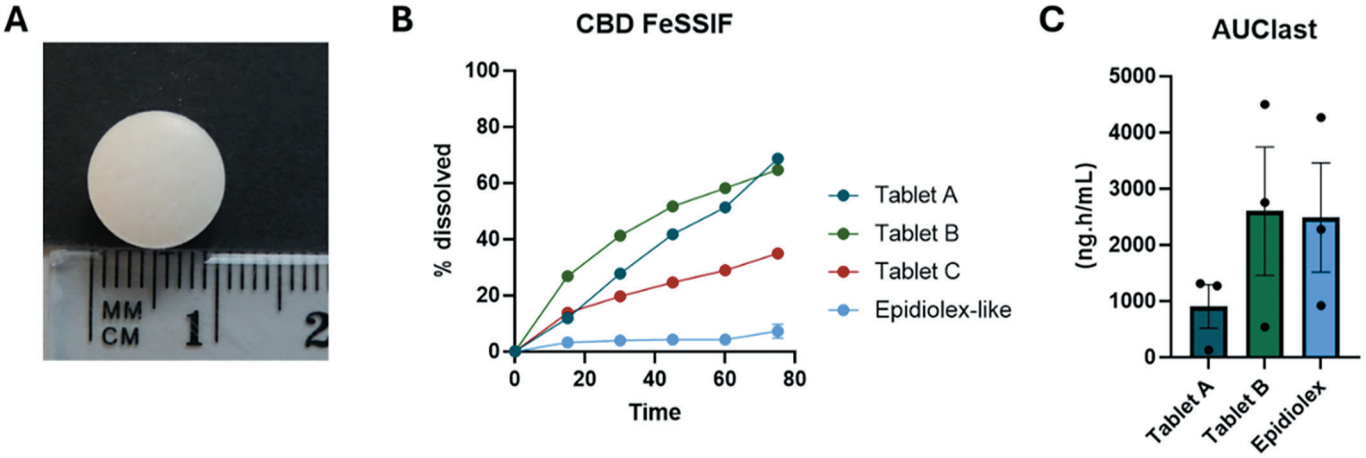

Figure 2. A: Representative tablet form of ART12.11 containing 100 mg CBD. B: FeSSIF CBD dissolution profiles from prototype tablets and an Epidiolex®-like solution. C: AUC of ART12.11 tablets and Epidiolex® in dogs

excipients evaluated are common and regulatory acceptable within the industry, with the majority having GRAS status. Differences in formulations were related to drug loading (up to 30%), precipitation inhibitor, disintegration agent, glidant and filler. Following initial screening, three lead prototypes (A, B and C) were taken forward for dissolution studies (comparing against an Epidiolex®-like formulation) and *in vivo* PK studies, where male Beagle dogs (n=3) were administered a single tablet of ART12.11 (100 mg CBD p.o., equivalent to 10 mg/kg) or Epidiolex® (10 mg/kg p.o.) in the fed state. Plasma samples were analysed for CBD and TMP by LC-MS/MS. **Results:** In FaSSIF, CBD release from prototype tablets was about 20% reflecting CBD's poor solubility in the absence of surfactants. In FeSSIF, CBD release was around 65% from tablets A and B, compared to 7% from an Epidiolex®-like solution after 75 min (Figure 2B). Preliminary data from ongoing PK studies suggest at least one of the lead formulations (Tablet B) leads to similar CBD exposure to Epidiolex® in dogs (Figure 2C). **Conclusions:** ART12.11 could represent a revolutionary approach using a patented form of CBD to effectively address large population indications such as generalised anxiety disorder. For pharmaceutical companies this represents a scalable, protected, low-cost approach for CBD in conditions previously seen as «out-of-scope». For patients, they would be able to use a simple and familiar conventionally sized tablet containing up to 150 mg of CBD. **Keywords:** Cannabidiol, pharmacokinetics, pharmaceutics, dissolution, cocrystal.

L-24

PEP: Leveraging Real-World Evidence for Advancing Cannabis-Based Medicinal Product Therapies

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Introduction: Advancing medical cannabis research is hindered by limited high-quality clinical trial data and restrictive guidelines for cannabis-based medicinal products (CBMPs). Real-world evidence (RWE) offers a practical solution to supplement randomized controlled trials (RCTs), particularly for herbal medicines. The Physicians Experience Platform (PEP) by Copeia was developed to address these challenges by collecting, analyzing, and presenting structured medical case studies through innovative visualization tools. **Aims:** The PEP platform aims to bridge gaps in medical cannabis research and therapy by providing a comprehensive framework for documenting and sharing real-world treatment experiences. It seeks to standardize the evaluation of CBMPs and support individualized therapy approaches while fostering collaboration among medical professionals. **Methods:** PEP leverages an interactive digital platform to document patient cases across four key pillars: patient anamnesis,

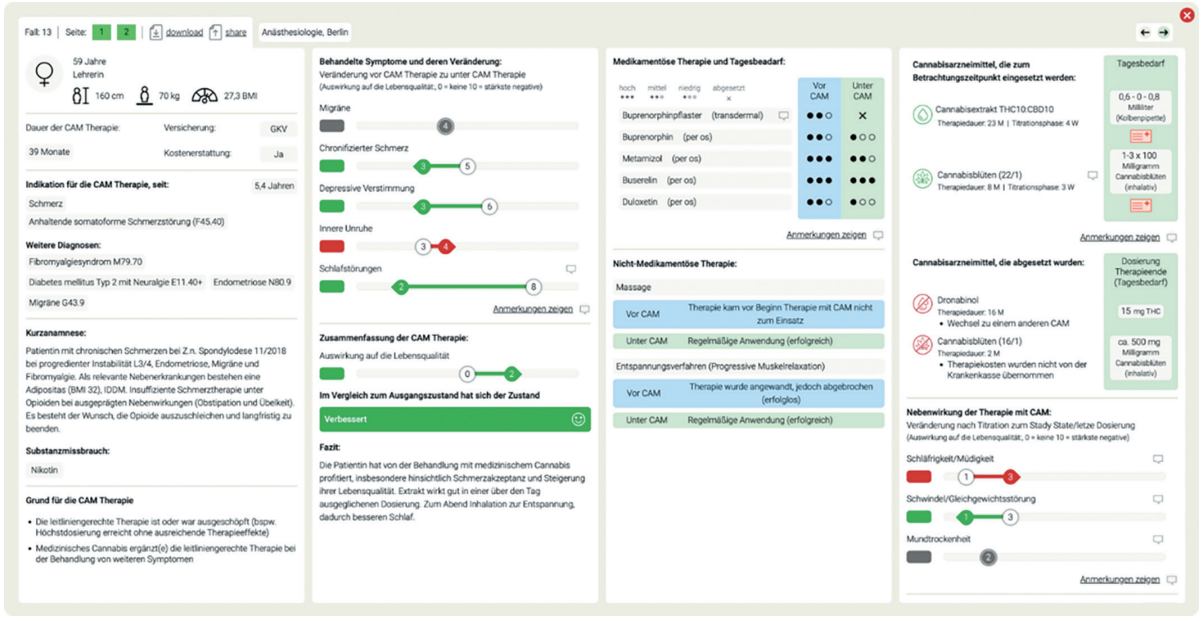

Fig. 1. PEP Case Card

symptom management and outcomes, therapies (both pharmacological and non-pharmacological), CBMP usage including dosages and side effects. This comprehensive data collection approach, aligned with the CARE (CAse REport) Guidelines, facilitates an in-depth understanding of therapy outcomes and highlights how specific CBMP treatments and dosage adjustments have improved practices. Anonymized patient data is analyzed through interactive data visualization tools, enabling users to navigate and interpret complex information with ease. The platform provides downloadable PDF case cards (Fig. 1) for sharing findings with colleagues or integrating into presentations. All submitted case data is reviewed and validated by a scientific team to ensure accuracy and adherence to clinical standards. **Results:** PEP has emerged as a scalable and practical solution to generate clinically meaningful data for CBMPs. The platform's structured approach to documentation addresses gaps in RCT data and enhances therapy standardization. PEP provides structured insights into CBMP therapy outcomes, allowing physicians to compare clinical aspects and share findings efficiently. The systematic presentation of data encourages collaboration and supports the broader adoption of CBMPs in clinical settings. **Conclusions:** The Physicians Experience Platform represents a pioneering step in advancing CBMP research and therapy. Through its structured approach, anonymized case reporting, and innovative visualization tools, PEP enhances the collection and interpretation of RWE, setting new standards for evidence-based cannabis medicine. **Keywords:** Digital health platform, real-world data, medical cannabis therapy, case study documentation, evidence-based therapy.

L-25

Reporting System MeCanna – Features, Challenges and Opportunities

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Introduction: On August 1, 2022, the ban on cannabis for medical purposes in Switzerland was lifted in the Narcotics Act and the treatment with cannabis-based medications no longer required am exceptional authorization by the Federal Office for Public Health. It is the responsibility of the physician to prescribe such products, including flowers, and thus it is not required to treat patients with other medications first. In order to be able to observe the development in treatment with cannabis and related number of prescriptions, an easy online reporting system «MeCanna» was established. Within the first few years after the law change came into effect, physicians who are prescribing medical cannabis are obliged to submit a mandatory report containing information related to the treatment. **Aims:** Keeping track of the prescriptions of cannabis and related products in Switzerland and gain further insights of the treated conditions as well as the effects of the interventions. **Methods:** The data collected by the reporting system was statistically analyzed. A total of 724 reports submitted by 384 users was included in the analysis of the first-year data. **Results:** The data of the first year of collection provides an overview of the parameters related to the treatment with cannabis and related medical products at the initiation of the therapy after the change in law. Compared to the number of permits issued before the change, only around 25% of prescriptions were reported. The majority of symptoms were

related to pain (52.2%), followed by sleep disturbances (12.7%), and spasticity (9.2%). The treated symptoms were associated with cancer in 12.1% of all cases, multiple sclerosis (7.2%) or migraine (7.2%). **Conclusion:** The «MeCanna» reporting system was developed to collect data related to the prescription of cannabis and related products. The analysis of the initial reports shows that the freedom of prescription did not have an influence on the treated conditions or the general treatment strategy. Subsequent analyses, including follow-up reports will provide further information about the progress of treatment. However, due to the large number of missing reports the results will be of limited value.

L-26

Country Report USA: Evidence Review Supporting United States Policy Change

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Introduction: The United States are experiencing rapid cannabis (marijuana) policy changes. **Aims:** We briefly summarize findings from an evidence synthesis of ten safety outcomes from medical and non-medical marijuana use and describe recent medical marijuana policy updates in the United States. **Methods:** Search strategies and screening procedures were developed using the Cochrane handbook. We searched 4 databases (PubMed, Embase, Cochrane, PsycInfo) in February 2023. Inclusion criteria: cannabis must be the treatment modality, patient-level controlled designs, quantitative measure of effectiveness or safety for the outcome. Exclusion criteria: publication before 2000, non-English, non-human research, the intervention is an FDA-approved cannabis-derived product, cannabis/cannabinoid formulations containing < 0.3% THC and/or topical formulations. Search records were screened by 2 independent reviewers, and a third resolved discordance. Studies underwent risk of bias assessment via the ROB2 tool for RCTs or the ROBINS-I tool for observational studies. Quality of evidence rating for outcomes was conducted via the GRADE approach. **Results:** We did not find high quality evidence supporting worsening in any indication, but most effectiveness evidence was rated as low quality. There were few serious adverse events reported in any studies across all indications and safety-specific outcome reporting was typically limited to counts of adverse events. For safety-specific results, 150 studies met all inclusion criteria and were reviewed, from 24,606 search records, with outcomes assessing the following: mortality, mental health, cognition, cancer, cardiometabolic risks, respiratory diseases, immunity, substance use disorders, and hyperemesis. Direction of findings in safety-specific studies were largely inconsistent, and no reviewed controlled observational studies were assessed as low risk of bias. **Conclusions:** Evidence quality was variable, but mostly of low quality, for outcomes assessed for indications. For outcomes assessed related to cannabis safety for any exposure type (medical or non-medical) within controlled observational studies, risk of bias was rated as high or critical in nearly all studies reviewed. Higher quality evidence can inform policies that reduce public health harm while maximizing potential benefit. Recent policy changes in the United States, where cannabis is undergoing reclassification from a Schedule I controlled substance to a less tightly regulated Schedule III, necessitate improved evidence quality. **Keywords:** Marijuana safety, medical marijuana effectiveness, medical marijuana evidence synthesis, United States medical marijuana policy. **Acknowledgments:** Funding for the evidence synthesis component summarized in this presentation is from the United States Food and Drug Administration (TO: #75F40123F19008), with material support from the Consortium for Medical Marijuana Clinical Outcomes Research. Content in this presentation does not necessarily represent the official positions, views, or policy of FDA, or the Consortium.

L-27

Country Report: Germany

C.F. Cimander[1]

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Germany's medical landscape has undergone significant changes since the legalization of medical cannabis in March 2017, which empowered doctors to prescribe it. Since then, the number of patients has been on a continuous upward trend, reaching approximately 300,000, and the research landscape has evolved considerably. However, there are still many obstacles to overcome in terms of acceptance for this new treatment. Health insurance companies very frequently reject coverage and threaten with economic sanctions for prescribing doctors. Many physicians remain critical of prescribing medical cannabis, partly due to a lack of knowledge and partly due to fundamental questions about whether it is medically indicated. After cannabis was no longer classified as a narcotic on April 1st, 2024, many telemedicine companies popped up, offering cannabis prescriptions without proper medical assessment and often without even seeing the patient. This had led to a blurring of the lines between medical use and recreational consumption, which is unfortunate. If we are serious about destigmatizing medical cannabis, it is essential that we strictly separate it from recreational use again. Nevertheless, medical cannabinoids represent a success story that is only just beginning in Germany. The ongoing development of innovative drug delivery systems is driving a shift towards more modern, ready-to-use pharmaceutical therapies. However, this also means that flowers are becoming less and less valued. Cannabinoid therapy is proving to be a valuable tool for many patients, and its potential to revolutionize treatment options across numerous medical disciplines is promising. Germany could thus become a pioneer for Europe. Future cannabis legislation will be pivotal in creating a clear divide between medical and recreational use. This will pave the way for greater adoption of evidence-based medicine among medical professionals.

L-28

Country Report: Spain

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The current landscape of medicinal cannabis in Spain is marked by gradual progress and ongoing debate. Although Spain has a long history of cannabis cultivation and use, the regulation of cannabis for medicinal purposes remains limited compared to other European nations. In June 2022, Spain's Congress approved recommendations to regulate medicinal cannabis, signaling a potential shift toward formalized frameworks for its use. However, the implementation of these recommendations has been slow, leaving patients and healthcare providers navigating a fragmented system. Currently, only market-authorized cannabis-based medicinal products Sativex® and Epidyolex® are available under strict conditions, requiring prescriptions through the Spanish Agency of Medicines and Medical Devices (AEMPS). Access is limited to specific indications, such as multiple sclerosis, and treatment-resistant epilepsy, with a focus on last-resort therapies. Despite this, many patients turn to cannabis associations or the black market to obtain products, raising concerns about safety, quality, and consistency. To date, a royal decree has been drafted by the Ministry of Health and allegations were allowed until November 2024. The Spanish medicinal cannabis access scheme, announced for end of this year, is expected to be stringent, with limited indications and pharmaceutical presentations allowed (only extracts, no dried flower), prescription by specialist doctor only and hospital dispensation, although this last feature has encounter significant resistance by patients and pharmacists altogether.

L-29

Country Report: Latin America - Medical Cannabis Regulation in Latin America: A Comparative Analysis

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Introduction: Latin America has seen significant changes in medical cannabis legislation over the past decade, with several countries implementing regulatory frameworks to allow access to cannabis-based treatments. **Aims:** To compare and analyze the current state of medical cannabis regulations across key Latin American countries, highlighting similarities, differences, and challenges in implementation and patient's access. **Methods:** A comprehensive review of medical cannabis legislation, regulatory frameworks, and implementation status was conducted for Colombia, Mexico, Ecuador, Uruguay, Chile, Brazil, Peru, Argentina, and Panama. Data was collected from government sources, peer-reviewed literature, and industry reports up to Nov. 2024. **Results:** All studied countries have legalized medical cannabis, with Uruguay being the first in 2013 and Panama the most recent in 2021. Regulatory approaches vary: Colombia, Uruguay, Chile and Argentina allow personal cultivation; Brazil strictly controls THC content (< 0.2%); Argentina, Mexico, Perú, Colombia, and Ecuador strictly control THC content (< 1%). Most of the countries face challenges in patient access despite established frameworks. Panama's program, while legalized, is not yet operational. Common features include prescription requirements, licensed pharmacy distribution, and government oversight. Unique aspects include Uruguay's state-controlled model and Argentina's REPROCANN patient registry. **Conclusions:** While medical cannabis is legally permitted across the region, significant variations exist in regulatory frameworks and implementation. Common challenges include limited patient access, high costs, and developing distribution infrastructure. Future research should focus on harmonizing regulations and improving patient access across Latin America. **Keywords:** Medical cannabis, Latin America, regulation, patient access, comparative analysis.

References:

[1] De Souza MR et al. J Cannabis Res 2022; 4(33). https://doi.org/10.1186/s42238-022-00142-z
[2] Nazif-Muñoz JI et al. Int J Drug Policy 2024; 127: 104395. https://doi.org/10.1016/j.drugpo.2023.104395
[3] Ramírez-Méndez JF et al. (2024). Heliyon 2024; 10(7): e27068. doi:10.1016/j.heliyon.2024.e27068

L-30

Country Report: Latin America - Medical Cannabis Regulation in Latin America: A Comparative Analysis

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(Online lecture, abstract not available)

L-31

Non-medical Cannabis Use: First Results from a Swiss Pilot Trial (Cann-L)

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Introduction: The Swiss parliament allows scientific trials of non-medical cannabis sales from 2021 to 2031 to investigate the possible impact of a future legalisation. The trials must be local and can include up to 5'000 adults already using the drug. While the first trials were initiated by local authorities, private players have also seized the opportunity to develop more commercially oriented projects. In early 2025, seven studies are ongoing with cannabis sales made in pharmacies, social clubs or dedicated shops. **Aims:** The project of the city of Lausanne and Addiction Switzerland (Cann-L) has been designed to test a public health oriented not-for-profit sales model in view of a future cannabis legalisation. Such a model is unusual in very liberal Switzerland, but the pilot trials provide the unique opportunity to test this alternative to

existing sales models used for alcohol, tobacco, or medicines. A dedicated shop has been opened in the city centre and its staff has been trained to deliver harm reduction messages instead of increasing sales. The cannabis products are produced locally, controlled and their introduction is discussed with a board of experts. **Results:** After one year, 1'200 cannabis users have joined the project, many of them long term and heavy users. In addition to cannabis sales data, they provide the research team with information about their use and health behaviour every six month through a questionnaire. First data analysis suggests that despite an easier access to cannabis products, the level of use among participants has remained stable on average while the cannabis products are not only of better quality but also often of lower potency than those found on the black market. Vaporizing cannabis instead of smoking has also been promoted and an easily available access to medical support has been used by several participants. **Conclusion:** Early data suggests that a not-for-profit sales model could be an interesting public health approach to limit the potential harms associated with legal cannabis use. **Keywords:** Cannabis, non-medical, pilot trial, not-for-profit, Switzerland.

L-32

Hot Topics in Cannabis Research

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Currently, several cannabis-based medicines are available, primarily focusing on specific cannabinoids, such as THC (delta-9-tetrahydrocannabinol) and CBD (cannabidiol), as well as their formulations. Whole-plant cannabis products available in various forms, including dried flowers, oils, tinctures, and encapsuled dried extracts. These medicines are used to treat a variety of medical conditions, often where conventional treatments have been less effective. The multifaceted nature of cannabinoid medicines will be highlighted, emphasizing their complexity as multisubstance mixtures with alleged polypharmacology. While much attention has been given to major cannabinoids, like THC and CBD, far less is understood about the pharmacology of minor cannabinoids, which may play crucial roles in the therapeutic effects of cannabis. Based on a recent Swiss research initiative, different open question in medical cannabis medicines will be elaborated. A critical gap in current research is the need for a deeper understanding of the endocannabinoid system and its involvement in various diseases, as this knowledge is essential for determining the efficacy or inefficacy of cannabis-based treatments. To support the use of medical cannabis, not only high-quality cannabis medicines are required but also knowledge about indications in which they do not work therapeutically. Understanding the lack of efficacy is just as important as recognizing therapeutic effects. This is crucial to differentiate cannabis/cannabinoids from pseudo placebos. Summarizing the IMCCB-25, I will address the tension between evidence-based medicine, patient needs, anecdotal reports, and the interests of the cannabis industry, highlighting the challenges in balancing scientific rigor with the growing demand for cannabis products. This discussion will underscore the urgent need for more comprehensive research to guide effective and safe use of cannabis medicines.

Abstracts of Poster Presentations

P-1

Between Medicine and Recreation: Stakeholder Strategies for Boundary Work in Swiss Cannabis Policy

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Introduction: Cannabis policy developments worldwide typically follow separate tracks for medical and non-medical use, even in jurisdictions pursuing both forms of legalization. As these parallel regulatory frameworks evolve, understanding how stakeholders negotiate and maintain boundaries between these domains becomes crucial for effective policy development. **Aim:** Using Swiss cannabis policies as a case study, this study examines how stakeholders engage in boundary work related to medical and non-medical cannabis regulation and research. **Methods:** The current study uses thematic content analysis to analyze qualitative interview data collected from 18 stakeholders working in the field of cannabis policy in Switzerland (e.g. scientists, policy makers, pharmacists, physicians, cannabis producers, former and current employees of the Swiss Federal Office of Public Health (FOPH). **Results:** The study revealed two distinct forms of boundary work employed by stakeholders. First, conceptual boundary work emerged through stakeholders' use of discursive methods to legitimize medical cannabis as a scientific subject while positioning non-medical cannabis within the social/political domain. Second, structural boundary work manifested through institutional mechanisms, particularly in relation to health insurance reimbursement and pharmacy distribution. While insurance reimbursement served as a key structural element distinguishing medical from non-medical cannabis use, the use of pharmacies as distribution points in non-medical cannabis policy pilot studies was identified as problematic, potentially undermining the intended boundary between medical and non-medical domains. **Conclusions:** This study shows the complexity stakeholders face in their attempts to maintain boundaries between medical and non-medical cannabis systems. The findings highlight how relying on scientific discourse to legitimize medical cannabis, while keeping non-medical cannabis in the social/political sphere, may create artificial distinctions that does not reflect the complex reality of cannabis use. If policy makers aim to reduce blurred boundaries, they need to carefully consider how policy elements (such as pharmacy-based distribution channels for non-medical cannabis) may undermine intended separations between domains. Additionally, expanding insurance coverage for evidence-based medical cannabis use could help clarify the distinction between medical and non-medical use. Finally, enhanced education is needed, particularly for future healthcare professionals who may prescribe cannabis, to help them navigate these complex discursive and structural boundaries in practice. **Keywords:** Qualitative interviews, boundary-work, cannabis, legalization, medical cannabis. **Acknowledgement:** This work was funded by the Swiss Science Foundation (#IZSEZO-2L5942|L).

P-2

Medicinal Cannabis in Post-traumatic Stress Disorder Patients: Pitfalls and Obstacles

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Introduction: Medicinal cannabis (MC) has become a relevant therapeutic option for managing symptoms of post-traumatic stress disorder (PTSD), including anxiety, sleep disturbances, and hyperarousal. Despite its potential, implementing MC in clinical practice is fraught with significant challenges that impact adherence and treatment efficacy. **Aims:** This presentation aims to explore the key pitfalls and obstacles in the MC treatment of PTSD patients, with a focus on access, adherence, compliance, and risk management. It also emphasizes the importance of personalized therapeutic approaches to optimize outcomes. **Methods:** The discussion is informed by our clinical observations and an analysis of barriers affecting MC treatment for PTSD, including underreporting of adverse effects, lack of efficient therapeutic partnership, misuse, dependency, and variability in cannabis formulations. The importance of personalized strategies, dosing schemas, and patient education is examined alongside broader systemic issues such as stigma, doctor-patient relationships, clinician knowledge gaps, and regulatory constraints. **Results:** Challenges identified include: (1) Underreporting of adverse effects: Patients often fail to disclose side effects due to stigma, fear of discontinuation, or limited understanding, hampering accurate monitoring and dose optimization. (2) Problematic use patterns: Some patients avoid and/or ignore a mandatory follow-up, exhibit misuse, dependency, or addiction, undermining treatment goals. (3) Variability in cannabis products: Non-standardized dosing and diverse cannabinoid profiles complicate treatment uniformity and predictability of responses. (4) Delivery methods and co-morbidities: Tailored delivery methods (e.g. vaporizers, tinctures) and consideration of co-occurring psychiatric or substance use disorders are essential for effective management. Systemic barriers such as restrictive authorities approach, high cost of treatment, societal stigma, limited clinician education, and restrictive regulatory frameworks further hinder MC's integration into PTSD care. **Conclusion:** To address these challenges, a multidisciplinary approach is essential, including: (1) Enhanced patient education, and fostering open communication and mutual trust. (2) Clinician training to improve knowledge and develop effective treatment practices based on close monitoring. (3) Research to establish the best standardized dosing guidelines and long-term safety data. (4) Policy reforms to reduce stigma and unnecessary administration and improve access to MC therapies. Personalized MC therapy can significantly improve outcomes for PTSD patients by balancing therapeutic benefits with risk mitigation. **Keywords:** Medicinal cannabis, PTSD, personalized therapy, adherence, dependence/CUD.

P-3

Introduction and Authorisation of GMP and QM for Medicinal Cannabis

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Introduction: Due to legislative changes in Switzerland (but also in the EU), many companies would like to establish a GACP-compliant or GxP (GMP/GDP)-compliant quality and documentation system as a basis and foundation for the production and trade of and with medicinal cannabis as an API/active ingredient or GACP raw material. This is a opportunity, but also a major challenge! **Aim and Methods:** The challenge with such tasks is to describe and introduce the GMP, GDP/GSP-relevant processes and activities.

- Establishment of a GMP QM system with SOPs for Introduction of Good Manufacturing & Distribution Practice
- Creation of a large number of QM documents (SOPs, Forms)
- Ongoing support from QM Office
- Creation of higher-level documents - including VMP, Site Master File and process risk analyses
- Preparation of the official inspection.

Results: In a specific project, the first step towards GMP and a Swissmedic authorisation (practical example) was to gather all the necessary information in a GMP report/study. The aim of this was to classify the product (product type, intended use and specification), but also to determine the GMP starting point and GMP scope as well as to identify hazards with regard to possible impurities (chemical, physical or microbial). This GMP report was later added as an essential component of the applications for authorisation by Swissmedic. At the same time, initial instructions on the topics of quality management, documentation, production, storage, distribution and trade, quality control and personnel were drawn up during the implementation of the quality management system. In addition, a detailed risk analysis of the entire production process of the cannabis raw material was carried out to fully identify any as yet unrecognised defects and the resulting measures. For this purpose, the individual steps, from cutting the cuttings from the mother plants, to growing and cultivating, flowering and caring for the cannabis plants, to drying, sorting and packaging the raw material, were analysed and discussed in detail. The comprehensive hygiene master plan was defined as another important component of the authorisation during this phase. The hygiene master plan defines zones with different requirements for the various hygiene measures (in terms of dress code and personnel hygiene, personnel and material flow, structural design, cleaning of the premises and the necessary air quality). **Keywords:** QM-System, GMP, GDP, risk analysis, qualification and validation.

P-4

Unlocking the Full Potential of Cannabis Therapy by State-of-the-art Drug Product Introduction

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Introduction: Cannabidiol (CBD) is a well-established drug compound with a good safety and tolerability profile and a promising candidate in many therapeutic areas. However, the highly lipophilic compound CBD shows poor aqueous solubility and variable oral bioavailability due to significant food interaction (about 4-fold differences in fasted and fed state). Furthermore, administration as oily solution suffers from tolerability limitations especially in higher doses and a complicated administration regime which can lead to poor patient acceptance and compliance. Thus, an innovative CBD-drug product (granules and tablets) with improved solubility, robust bioavailability and improved usability for patients and medical professionals has been developed and the main pharmacokinetic parameters were assessed.

Aims:

- The aim of the presented clinical trial was the characterization of maximum systemic exposure of CBD of the newly developed CBD 30% granules (GRA, 1500 mg CBD per dose) in comparison of its systemic bioavailability to CBD administered as oily solution (CBD 10% oil, 100 mg/mL, 1500 mg CBD per dose).
- Comparison of relative bioavailability of CBD 30% GRA *vs.* CBD 10% oil after multiple dose admini-stration after a light meal determined by use of area under the curve (AUC) 144-168, steady-state (ss), C_{max},144-168, ss, and C_{min},144-168, ss of CBD.

Secondary objectives:

- Characterization of pharmacokinetics of CBD 30% GRA (test, 1500 mg CBD) and oily CBD 10% oil (100 mg/mL), after multiple dose administration after a light meal determined by the relevant pharmacokinetic parameters of CBD.
- Descriptive characterization of safety and tolerability of CBD 30% GRA and CBD 10% oil in the study population.

Conclusions:

- Systemic exposure under steady state conditions was nearly identical for both products considering AUC144-168, ss, C_{max},144-168, ss, and C_{min},144-168, ss of CBD.
- CBD 30% GRA were safe at the dosage studied over the period of use. The observed side effects were of mostly mild to moderate intensity, clinically irrelevant and reversible in all cases.

In Summary, a patient friendly and state-of-the-art CBD-drug product has been developed and the bioequivalence to CBD oil has been demonstrated. This new CBD-drug product can be used for highly standardized clinical studies. **Keywords:** Finished drug, cannabinoid based drug technology platforms, innovative dosage form, advanced drug delivery system.

P-5

Medical THC, Driving, and Road Safety: The Point of View of Traffic Medicine

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Introduction: Interest in cannabis-based medicines (CBMs) has risen importantly in recent years due to the wide range of potential uses. The reasons are many and can be difficult summarized. Among the most cited reasons, it is worth mentioning a greater request from patients for so-called «alternative» remedies to traditional pharmacological treatments, as well as a different perspective on the disease and the solution that physicians should propose for the treatment. However, delta-9-tetrahydrocannabinol (THC) impairs driving performance and other safety-sensitive tasks. **Aims:** The aim of this paper is to briefly discuss current Swiss legal issues concerning CBMs and fitness-to-drive medical assessment. **Methods:** Under the Swiss Narcotics Act, use of cannabis with a THC content of at least 1% is generally prohibited. The Swiss Parliament has however decided to lift the ban on CBMs from August 1, 2022. Exceptional authorisation from the Federal Office of Public Health is therefore no longer required for CBMs prescription. Accordingly, general practitioners may prescribe CBMs irrespective of the medical diagnosis. Prescribing physicians must still inform their patients that these medicines may affect momentary and general fitness-to-drive. **Results:** The positioning of cannabis as a legitimate medical treatment produces some tensions with other regulatory frameworks. A notable example of this is the so-called «zero tolerance» drug driving legal frameworks, which criminalise the presence of THC in a driver's bodily fluids irrespective of impairment. Indeed, it has been observed that there is little evidence to legitimate the differential treatment of patients taking CBMs compared with those taking other psychotropic medications potentially impairing fitness-to-drive. **Conclusions:** Patients using CBMs should be advised to avoid driving during the initiation of treatment and in the hours immediately following each dose. Patients using CBMs should also be informed that they are at risk of testing positive for cannabinoids in oral fluid and/or in urine. Fitness-to-drive medical assessments might be required by the authorities in doubtful cases based on the results of toxicological analyses, regardless of whether driving is not impaired at the time of the police check. **Keywords:** Medical THC, driving, medical fitness-to-drive, traffic medicine, toxicology.

P-6

The Importance of Multi-effect of Medical Cannabinoids in Different Indications: A Case Series in a Primary Care Setting

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Introduction: The multi-effect potential of medical cannabinoids (analgesic, anti-inflammatory, anticonvulsant, antiemetic, anxiolytic, sleep modulation and appetite-stimulating properties) has positioned them as a valuable therapeutic option in managing complex and multifaceted medical conditions [1]. However, the clinical evidence supporting multi-benefits is poor. **Aims:** In our dispensary unit within a primary care setting with a specialized consultation for medical cannabis for over 20 years, we have had multiple clinical situations of patients who requested medical cannabinoids for various somatic and psychological conditions. We present hereby some typical situations and focus on clinical improvement and deprescribing other drugs. **Methods:** Case series of 3 patients treated with medical cannabinoids at our unit. Data from medical records on prescribed cannabinoids, dosage, treatment duration, and clinical outcomes were analyzed. **Results:** *Case 1:* 85-years-old woman with a known history of diabetes and refractory chronic polyneuropathic pain, on tramadol 100 mg/day, anxiety disorder, and sleep disturbances. Treatment with a CBD-dominant formulation resulted in significant pain relief, improved sleep quality and cessation of opioids use (Table 1). *Case 2:* 45-years-old woman suffering from post-traumatic stress disorder with no improvement despite regular psychiatric follow-up. She started smoking cannabis with a beneficial effect. Treatment with THC-CBD oily formulations resulted in significant reduction of anxiety and flashbacks, of sleep disorder and cessation of cannabis smoking (Table 1). *Case 3:* 42-years-old man suffering from severe anxiety disorder, severe alcohol dependency, and sleep disturbances, resistant to multiple conventional treatments. A THC-CBD formulation resulted in a complete cessation of alcohol consumption, important reduction of benzodiazepine use and significant mood improvement (Table 1). **Conclusions:** Medical cannabinoids have significant multi-effect properties to reduce refractory symptoms across multiple domains (pain, anxiety, sleep), improve quality of life and enable in some cases deprescription of other pharmacological treatments. By addressing multiple symptoms concurrently, medical cannabinoids represent a promising adjunct or alternative therapy, particularly in primary care for patients with chronic conditions, where conventional treatments fall short. **Keywords:** Medical cannabinoids, multi-effect, chronic pain, anxiety, deprescription.

Reference:

[1] Bilbao A., Spanagel R. Medical cannabinoids: a pharmacology-based systematic review and meta-analysis for all relevant medical indications. BMC Med 2022; 20: 259.

P-7

Clinical Study Design for a Randomized, Open-label, 4-Way Crossover, Pharmacokinetic Study Comparing a Solid to an Oily Cannabidiol Formulation Under Fasted and Fed Conditions

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Introduction: Cannabidiol (CBD) is an effective API for the treatment of epilepsy in children. The current marketed drug is an oily solution. For clinical practice, a tablet is considered more patient-friendly. Therefore, > 160 different solid formulations of CBD have been produced and tested *in vitro*. A spray-dried nano-emulsified prototype was selected for the planned pharmacokinetic (PK) study. **Aims:** The aim was to generate a robust clinical study design to compare an oily to a solid CBD formulation. **Methods:** ICH GCP guidelines with integrated Addendum E6 (R2) were applied.

Table 1. Description of case series

Clinical Cases	Background	Treatment	Outcomes	Comments
Case 1	Chronic pain Anxiety Sleep disorders Opioids use	38 mg CBD per day THC <0.5%	80% reduction in pain scores (VAS scale) Improved sleep duration and quality Cessation of opioids use	The combination of analgesic, anxiolytic and effects on sleep quality demonstrates the multi-effect of CBD
Case 2	PTSD Cannabis use disorder	2.7 mg THC, 2.5 mg CBD per day	Significant reduction of anxiety and flashbacks Improved sleep quality. Cessation of tobacco and cannabis smoking	The anxiolytic effects of THC and CBD enabled different benefits: a significant improvement of quality of life and smoking cessation
Case 3	Severe anxiety disorder Alcohol use disorder Benzodiazepine use disorder	10 mg THC, 10 mg CBD per day	95% reduction benzodiazepine use 90% reduction cravings Cessation alcohol consumption 20% reduction anxiety 80% sleep improvement	The combination of anxiolytic, Anti-craving and effects on sleep quality demonstrates multi-effect of THC and CBD

Results: Assessing the PK properties of the solid CBD formulation in healthy adults compared to an oily formulation using the $AUC_{0\text{-}24h}$ of the CBD plasma concentration in fed and fasted state after single administration of CBD was defined as primary objective. From previous clinical CBD studies, it is known that oral CBD bioavailability is very low and plasma CBD clearance is very high. Therefore, the PK properties of the plasma metabolites of CBD, 7-hydroxycannabidiol (7-OH-CBD) and cannabidiol-7-oic acid (7-COOH-CBD) were included. Furthermore, the $AUC_{0\text{-}24h}$ sums of all measured plasma levels of CBD, 7-OH-CBD, and 7-COOH-CBD were covered in the objectives. All PK parameters: C_{max}, T_{max}, $T_{1/2}$, $AUC_{0\text{-}24h}$, and AUC_{inf} will be determined. The power calculation allowed for N=32 subjects. The 16 males and 16 females will be randomly assigned into 4 groups that will be equally distributed into 4 treatment regiments in open-label, 4-way crossover design. **Conclusions:** The PK study design was defined according to GCP standards. **Keywords:** CBD formulations, pharmacokinetics.

P-8

Monoacylglycerol Lipase Activity is Increased in the Periphery But Not in the Central Nervous System of a Mouse Model of Chemotherapy-induced Neuropathic Pain

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Introduction: The use of paclitaxel against cancer is limited by development of chemotherapy-induced neuropathic pain (CINP). The endocannabinoid 2-arachidonoyl glycerol (2-AG) has antinociceptive activity, however it is rapidly metabolised by the enzyme mono-acylglycerol lipase (MAGL). Recently, we observed that there is a deficiency of 2-AG in the paw skin, but not in the spinal cord or brain of mice with paclitaxel-induced mechanical allodynia [1]. Administration of MAGL inhibitors both systemically and locally in the paw skin alleviated paclitaxel-induced mechanical allodynia [1, 2]. **Aims:** The aims of this study were to evaluate (1) whether there are differences in MAGL protein expression and activity in the periphery (paw skin), and CNS (spinal cord and brain) of mice with paclitaxel-induced mechanical allodynia, (2) if prophylactic treatment with a triterpene MAGL inhibitor (pristimerin) prevents the effects of paclitaxel and, (3) if 2 triterpenes found in *Cannabis sativa*, friedelin and epifriedelanol [3], had similar binding affinity to MAGL compared to pristimerin. **Methods:** The effects of treatment of female BALB/c mice with pristimerin intraperitoneally on paclitaxel-induced mechanical allodynia were measured using the dynamic plantar aesthesiometer. MAGL protein expression in the mouse tissues was measured using Wes™ and the enzyme activity was measured using MAGL activity fluorometric assay kit. Molecular docking was performed using CB-Dock2. **Results:** Pristimerin prevented paclitaxel-induced mechanical allodynia. Paclitaxel treatment increased MAGL protein expression only in the brain. MAGL activity was increased in the paw skin, but not in the spinal cord and brain, of mice with paclitaxel-induced mechanical allodynia. Pristimerin prevented the paclitaxel-induced increase in MAGL activity. The Vina scores obtained from molecular docking for the 3 triterpenes were pristimerin (-10.2 kcal/mol), friedelin (-9.9 kcal/mol), and epifriedelanol (-9.9 kcal/mol). **Conclusion:** During paclitaxel-induced mechanical allodynia there is an increase in MAGL activity in the paw skin, that possibly contributes to the deficiency of 2-AG in the paw skin, but not in the spinal cord or brain. Treatment with triterpene MAGL inhibitors could be useful in the management of CINP, by inhibiting the increased enzyme activity in the periphery. Triterpenes found in *Cannabis sativa* warrant further studies as MAGL inhibitors. **Keywords:** Triterpenes, MAGL activity, neuropathic pain, endocannabinoid, 2-arachidonoyl glycerol. **Acknowledgements:** This work was supported by grant PT02/23. We thank Ahmad Barakat, Aisha Albaloushi, Amal Thomas, Esraa Aly, and Liny Jose for technical assistance.

References:

[1] Thomas A, Okine BN, Finn DP, Masocha W. Peripheral deficiency and antiallodynic effects of 2- arachidonoyl glycerol in a mouse model of paclitaxel-induced neuropathic pain. Biomed Pharmacother 2020; Sep; 129: 110456. doi: 10.1016/j.biopha.2020.110456.

[2] Al-Romaiyan A, Masocha W. Pristimerin, a triterpene that inhibits monoacylglycerol lipase activity, prevents the development of paclitaxel-induced allodynia in mice. Front Pharmacol 2022; Aug 9; 13: 944502. doi: 10.3389/fphar.2022.944502.

[3] Slatkin DJ, Doorenbos NJ, Harris LS, Masoud AN, Quimby MW, Schiff PL Jr. Chemical constituents of *Cannabis sativa* L. root. J Pharm Sci 1971; Dec; 60(12): 1891-2. doi: 10.1002/jps.2600601232.

P-9

Antiproliferative Effect of Phytochemicals from *Cannabis sativa:* New Hope for Colorectal Cancer Therapy?

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Introduction: Colorectal cancer (CRC) is a widespread and deadly disease, causing nearly 1 million annual deaths due to cancer invasion and metastasis [1]. *Cannabis sativa* has been recommended in cancer therapy to reduce pain and symptoms associated with common chemotherapy. However, there are emerging evidence that phytochemicals found in this plant, namely cannabinoids, terpenes and flavonoids, may also inhibit tumor proliferation and growth, highlighting their potential as co-adjuvant agents in cancer therapy [2, 3]. **Aims:** Evaluation of the antiproliferative activity of several cannabinoids, terpenes and flavonoids, present in *C. sativa,* using 2D and 3D cell models of CRC. **Methods:** Antiproliferative effect of 18 cannabinoids, 6 terpenes and 3 flavonoids were assessed in 2 CRC cell lines - HT29 and LoVo - using monolayer cultures (2D model) and cell spheroids generated in stirred culture systems, constituting more physiologically relevant cancer models (3D cell models). Confluent Caco-2 cells were used as a model of intestinal epithelium, to investigate the gastrointestinal safety of these compounds.

Results: Most of the compounds exhibited antiproliferative effect in both cell lines, this effect being more pronounced in LoVo cells which are derived from a CRC metastasis. In general, cannabinoids and flavonoids showed higher antiproliferative effect compared to terpenes. Among all, Δ^9-THC, CBD, CBDA and cannflavin B demonstrated the highest antiproliferative effect in both 2D and 3D cell models of HT29 and LoVo cells (EC_{50} = 10.4 – 46.4 μM) combined with no cytotoxicity in Caco-2 cells (IC_{50} > 60 μM). The antiproliferative effect of these compounds decreased in 3D cell models (increases of EC_{50} up to 6.7 times) what could be explained by the phenotypic characteristics of cell spheroids and/or diffusion limitations of the compounds through spheroids. Nevertheless, these results are within the values obtain for chemotherapeutic drugs like oxaliplatin, irinotecan and 5-fluoruracil (EC_{50} = 9.2 – 917 μM). Among terpenes, α-humulene and b-caryophyllene were the most effective compounds (EC_{50} < 140 μM). **Conclusions:** This research presents new relevant insights into the anticancer potential of cannabis-derived compounds and will contribute to the rational design of extraction processes of the compounds with improved bioactivity from cannabis plant for CRC prevention and therapy. **Keywords:** Cannabinoids, terpenes, flavonoids, colorectal cancer, antiproliferative potential. **Acknowledgments**: Fundação para a Ciência e a Tecnologia/Ministério da Ciência, Tecnologia e Ensino Superior (FCT/MCTES, Portugal) through iNOVA4Health (UIDB/04462/2020andUIDP/04462/2020), Associate Laboratory LS4FUTURE (LA/P/0087/2020), PhD fellowships (2023.02451.BDANA and 2021.07620.BD) and EEC contract grant (CEECIND/04801/2017).

References:

[1] Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2024; 74(3): 229-63.
[2] Silva-Reis R, Silva AMS, Oliveira PA, Cardoso SM. Antitumor Effects of *Cannabis sativa* Bioactive Compounds on Colorectal Carcinogenesis. Biomolecules 2023; 13(5): 764.
[3] Filipiuc LE, Ababei DC, Alexa-Stratulat T, Pricope CV, Bild V, Stefanescu R, et al. Major Phytocannabinoids and Their Related Compounds: Should We Only Search for Drugs That Act on Cannabinoid Receptors? Pharmaceutics 2021; 13(11): 1823.

P-10

Altered Endocannabinoid Signaling Might Contribute to Obesity in P62 KO Mice

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Introduction: The cannabinoid receptor 1 (CB1R) plays a crucial role in obesity by regulating energy metabolism, food intake, and fat accumulation. Recently, we have discovered an interaction between the endocannabinoid system and the adapter protein p62 [1-3]. P62 knockout (KO) mice exhibit obesity, insulin resistance, and leptin tolerance [4]. Loss of p62 leads to increased basal ERK activity, fostering increased adipogenesis, potentially explaining the obesity observed in p62 KO mice [4]. As a cargo protein involved in autophagy, p62 may facilitate the degradation of CB1R via the autophagosomal-lysosomal pathway. This could lead to a reduction in CB1R levels and subsequently affect cannabinoid signaling. Here, we have investigated whether hypothalamic CB1R expression or endocannabinoid levels are altered in p62 KO mice and thus could contribute to the development of high body weight. **Aims:** This study aims to investigate the molecular interplay between p62, the endocannabinoid system, and CB1R signaling in the regulation of energy balance and metabolic homeostasis. Specifically, we sought to determine whether p62 deficiency leads to altered CB1R expression, endocannabinoid levels, and CB1R protein turnover via the autophagy pathway, and how these alterations contribute to the development of obesity in p62 KO mice. **Methods:** We tracked the daily food intake of p62 KO and wild-type (WT) animals during the period when p62 KO mice typically become overweight. We monitored their home cage activity and measured their body weight. CB1R protein levels were assessed using Western blot, while hypothalamic 2-arachidonoylglycerol and anandamide (2-AG and AEA) levels were measured using LC-MS/MS in p62 KO and control tissue samples. In WT cortical neurons, we quantified CB1R protein turnover after inhibiting autophagy. **Results:** P62 KO animals become obese around 4 months of age, despite consuming a similar amount of food as WT animals. Interestingly, 3 weeks before obesity onset, KO mice reduced their activity, resembling CB1R activation. We therefore investigated whether increased endocannabinoid or CB1R levels contribute to this phenomenon. We found elevated 2-AG levels in the hypothalamus of p62 KO animals, with no differences in CB1R protein levels in brain tissues. However, in WT mouse neurons, we observed that inhibiting autophagy with bafilomycin significantly blocked CB1R degradation, demonstrating that CB1R protein turnover is mediated by autophagy. **Conclusions:** The notable decrease in home cage activity predisposes the animals to obesity, even without increased food consumption at 4 months of age. Our findings suggest that alterations in the endocannabinoid system occur in p62 KO mice, potentially influencing the development of the obesity phenotype. **Keywords:** p62 knockout mice, CB1 receptor, obesity, autophagy.

References:

[1] Keller C et al. Cells 2022; 11: 1517
[2] Keller C et al. Front Pharmacol 2022; 13: 858215
[3] Sharaf A et al. Front Mol Neurosci 2019; 12: 224
[4] Rodriguez A et al. Cell Metab 2006; 3: 211

P-11

Add-on Treatment with Cannabis Extract in Cauda Equina Syndrome (CES): Case Report

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Introduction: The Cauda Equina Syndrome (CES) can result in chronic neuropathic pain (NP), affecting patient's quality of life. Symptoms include severe lower back pain, numbness, weakness, bladder, bowel and sexual dysfunction. The endocannabinoid system (ECS) plays a vital role in NP pathophysiology, making it an important target for refractory NP treatment. Emerging evidences suggest that medical cannabis may alleviate NP and improve Total Pain (TP), that encompasses emotional, social and spiritual aspects in addition to physical pain. **Aim:** Reporting a case of individual experimental treatment of refractory NP with medicinal cannabis in a patient with CES. **Methods:** Six months post-surgery for extruded LDH a 36-year-old female reported continuous severe NP in her left leg (Visual Analogue Scale [VAS] = 10), accompanied by urinary and fecal incontinence, depression, and insomnia. She was on pregabalin (300 mg), duloxetine (60 mg), and methadone (20 mg) daily, suffering from significant side effects. Following good medical practices and bioethics framework we implemented an oral complementary treatment with a full-spectrum oil registered in Brazil (CBD 75 mg/mL, THC 9 mg/mL), starting with CBD 7.5 mg, THC 0.9 mg per day, and increasing every 5 days until a preestablished result of 70% pain relief. **Results:** After 1 month, her VAS improved to 5, with enhanced sleep and activity levels. Four months later, VAS decreased to 3, allowing for medication reductions. By 1 year, VAS was at 2, with continued use of pregabalin (150 mg) and 75 mg CBD : 9 mg THC. After 3 years, VAS remain at 2. Patient refers 80% improvement in TP and in quality of life, with no side effects. **Conclusions:** Refractory NP can be significantly improved with medical cannabis as an adjunct therapy. It effectively targets pain pathophysiology and related comorbidities, enhancing overall TP. Additionally, the favorable safety profile referred by the literature suggest the need of more standardized, randomized, long-term studies for greater evidence. **Keywords:** Refractory neuropathic pain, medical cannabis.

P-12

Phytocannabinoids Therapy for MASLD: Lipidomics and Metabolomics Perspective

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Introduction: Metabolic dysfunction-associated steatotic liver disease (MASLD) remains a prevalent condition without approved pharmacological treatments. Cannabidiol (CBD) has demonstrated efficacy in reversing obesity-induced hepatic steatosis and dyslipidemia, independent of body weight changes. Cannabigerol (CBG), another promising phyto-cannabinoid, may have similar therapeutic potential, though its role in MASLD is less explored. **Aims:** This study aimed to uncover the molecular mechanisms underlying the therapeutic effects of both CBD and CBG in ameliorating MASLD. **Methods:** A high-fat diet (HFD)-induced obese mouse model was treated with CBD (5 mg/kg/day, IP) or CBG (12.5 mg/kg/day, IP) for 4 weeks. Comprehensive lipidomics (> 2100 lipids, including 56 lipid species) and metabolomics (367 metabolites) analyses were conducted. Metabolic assessments and enzymatic activity were evaluated to uncover the mechanisms driving the observed therapeutic effects. **Results:** Both CBD and CBG treatments significantly reversed hepatic steatosis, improved dyslipidemia, and reduced insulin resistance. Metabolomic analysis revealed minimal alterations in energy metabolism but demonstrated an enhancement in the creatine-phospho-creatine system, a critical pathway for hepatic energy homeostasis. Lipidomic profiling identified key changes across multiple lipid classes, including increased phosphatidylcholines (PCs), indicative of enhanced very-low-density lipoprotein (VLDL) secretion. Elevated levels of lysobisphosphatidicacids (LBPAs), crucial for the late endosome-lysosome system and cholesterol trafficking, were also observed, potentially explaining the reduction in hepatic lipid accumulation. **Conclusion**: Our study highlights the therapeutic potential of CBD and CBG in mitigating MASLD by alleviating hepatic steatosis and improving metabolic regulation. Key molecular mechanisms include enhanced lipid excretion and an increased phosphocreatine energy reservoir. These findings provide valuable insights into phytocannabinoid-based therapies and highlight innovative strategies for managing MASLD and related metabolic disorders. **Keywords:** MASLD, phytocannabinoids, metabolomics, lipidomics.

P-13

The Role of Phytocannabinoids in Triple Negative Breast Cancer

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Introduction: Breast cancer is the most frequently diagnosed cancer in women worldwide. Triple-negative tumors (TNBC) are deficient for well-defined molecular targets making chemotherapy, which is non-specific and cytotoxic, the most common treatment option [1-3]. Hence, there is a need for innovative therapeutic interventions to help women with breast tumors. Cannabinoids are products of *Cannabis sativa*. They were first introduced as palliative medicinal products, aiding in reducing emesis resulting from chemotherapy for cancer patients. Cannabinoids possess anti-tumoral activity in breast cancer cell lines. **Aims:** In this study,

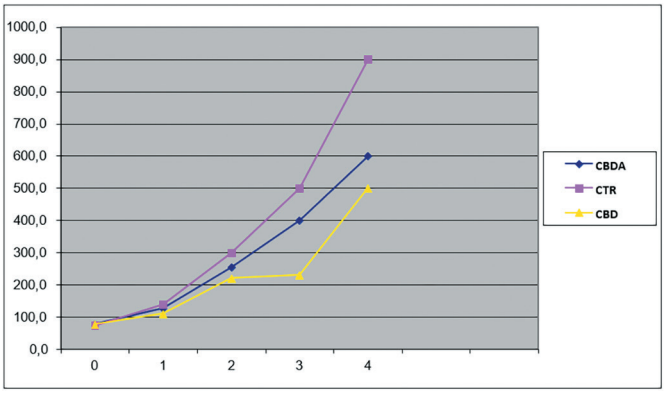

Figure 1. CBD and CBDA reduce the tumor growth in the TBNC mouse model. CBD and CBDA promote tumor growth in breast tumor xenograft models. Breast tumor growth in mice treated with vehicle, CBD, and CBDA. Tumor volumes reduced after 28 days of CBD and CBDA treatment until 35 days ($P < 0.05$) as compared with control (vehicle-treated).

to elucidate the role of cannabidiol (CBD) and cannabidiol acid (CBDA) in tumor growth progression in TNBC, we performed *in vitro* studies on MDA.MB231 cells, and *in vivo* studies on heterotopic mice of TNBC. **Methods:** *In vitro* assays were performed on triple-negative MDA-MB-231 cells treated with CBD and CBDA, alone and in combination. The effects of CBD and CBDA on viability were determined by wound healing and MTT assays, and cell migration was assessed by transwell migration and *in vitro* apoptosis by flow cytometry. A subcutaneous injection of MBA. MB231 cells into the right-side flank area of BALB/c mice generated xenograft mouse model of TNBC. After the randomization mice were divided into 3 groups according to the different types of treatment: (1) normal saline (vehicle); (2) CBD and (3) CBDA injected peri-tumorally every day for 3 weeks. The animals were sacrificed 2 weeks later. Half of the tumor tissue was formalin-fixed and paraffin-embedded for immunohistochemistry for CD31, for immunofluorescence localization of Ki67 protein, and routine H&E staining. Western blotting analysis was performed according to standard protocols on protein extracted from breast tumor tissues to detect the expression of proteins P53 and Bcl2. **Results:** We demonstrated that both CBD and CBDA, can inhibit cell proliferation of MDA MB 231 cells by enhancing the apoptosis. *In vivo* studies performed on xenograft mouse model of TNBC, revealed that tumors of mice treated with CBD and CBDA are smaller than those observed in the controls (Fig. 1). CBD modifies the expression of tumor development markers Ki67, Bcl2 and P53. **Conclusions:** Our results suggest that CBD and CBDA, can be viewed as promising agents for inhibiting TNBC progression, which has scarce therapeutic options and is featured by inauspicious prognosis and low survival rates. **Keywords:** Cannabinoids, CBD, CBDA, triple negative breast cancer. **Acknowledgments:** The Authors are grateful to Dr. Alessandra Trocino, Mrs. Mariacristina Romano and Dr. Mariacinzia Grizzuti from Istituto Nazionale Tumori IRCCS Fondazione Pascale for providing excellent bibliographic service and assistance. This work was (partially) supported by the Italian Ministry of Health Ricerca Corrente Project M4/3. We thanks Dr. Ana Serrato from Avextrafor providing financial support.

References:

[1] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA and Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018; 68(6): 394-424. DOI: 10.3322/caac.21492.
[2] Lukong KE. Understanding breast cancer - The long and winding road. BBA Clin 2017; 7: 64-77. DOI: 10.1016/j.bbacli.2017.01.001.
[3] Bimonte S, Cascella M, Barbieri A, Arra C and Cuomo A. Shining a light on the effects of the combination of (-)- epigallocatechin-3-gallate and tapentadol on the growth of human triple-negative breast cancer cells. In Vivo 2019; 33(5): 1463-1468. DOI: 10.21873/invivo.11625.

P-14

Medicinal Cannabis: Extended Stability of Cannabis Extracts Produced Using a New Ethanol-based Extraction Method

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Introduction: Cannabis as a therapeutic agent is increasing in popularity all around the globe, particularly in Western countries, and its potential is now well assessed. On the other hand, each country has its own regulation for the preparation of cannabis macerated oils. In Italy, there are only a few preparation methods allowed [1-3]. **Aims:** With this work, we aim to perform a stability study of cannabis oils produced with a novel method for the extraction of cannabinoids from cannabis inflorescences. Three different varieties of cannabis were used, with and without adding tocopherol acetate as an antioxidant. **Methods:** Cannabinoids were extracted using ethanol at room temperature. Then, the solvent was evaporated under reduced pressure and the preparations reconstituted with olive oil. In this work, we assessed the stability of both cannabinoids and terpenes in these formulations over 8 months. Cannabinoid stability was assessed by monitoring the concentrations of THC and CBD, while terpene stability was assessed by monitoring β-caryophyllene and α-humulene concentrations. **Results:** Stability of the extracts was not influenced by the presence of tocopherol acetate, though refrigeration seems to be detrimental for a long storage of products, especially regarding THC concentrations (Fig. 1). **Conclusions:** The improvements offered by this method reside in the flexibility in controlling the concentration of the extract and the ability to produce highly concentrated oils, alongside the possibility to produce standardized oils despite the variability of the starting plant material. **Keywords:** Cannabis, Cannabaceae, stability, macerated oils, extraction, galenic formulations. **Acknowledgments:** The Authors are grateful to Mrs. Mariacristina Romano from Istituto Nazionale Tumori IRCCS

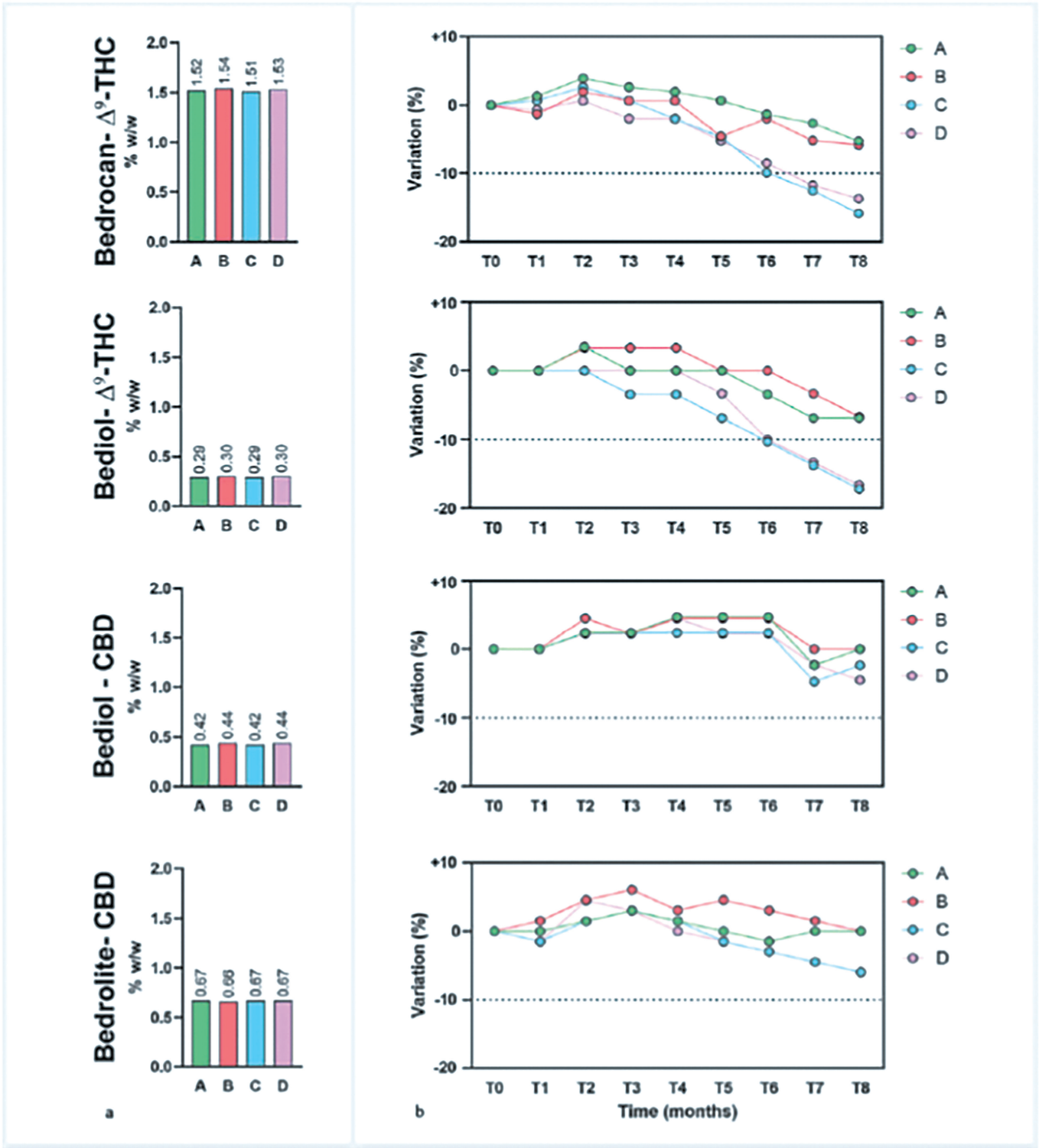

Figure 1. Panel A displays the concentrations (% w/w) of cannabinoids in each sample at the beginning of the study (T0); panel B displays the variation (%) of cannabinoids concentrations over time. Samples A were added with tocopherol acetate (0.05% w/v) as an antioxidant and stored at room temperature. Samples B were not added with an antioxidant and stored at room temperature. Samples C were added with tocopherol acetate (0.05% w/v) as an antioxidant and stored at refrigerated temperature. Samples D were not added with an antioxidant and stored at refrigerated temperature. The number after «T» refers to the months passed after the beginning of the study. Therefore, T0 indicates the beginning of the study, T1 one months later and so on.

Fondazione Pascale for providing excellent bibliographic service and assistance. We thanks Dr. Ana Serrato from Avextra for providing financial support.

References:

[1] Klumpers LE, Thacker DL. A brief background on cannabis: From plant to medical indications. J AOAC Int 2019; 102: 412-420. doi: 10.5740/JAOACINT.18-0208
[2] Borgelt LM, Franson KL, Nussbaum AM, Wang GS. The pharmacologic and clinical effects of medical cannabis. Pharmacotherapy 2013; 33: 195-209. doi: 10.1002/PHAR.1187
[3] Baron EP. Medicinal properties of cannabinoids, terpenes, and flavonoids in cannabis, and benefits in migraine, headache, and pain: An update on current evidence and cannabis science. Headache 2018; 58: 1139-1186. doi: 10.1111/HEAD.13345

P-15

Analysis of Cannabinoids by Interlabor Belp AG

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Introduction: In recent years, the legalization of cannabis has been pursued by more and more countries. It contains over 500 different substances, including more than 100 cannabinoids, some of which show psychoactive effects. The key psychoactive compound is Δ-9-tetrahydrocannabinol (THC), for which strict legal limits are imposed due to its pharmacological and toxicological properties. Another significant but non-psychoactive component is cannabidiol (CBD), which was classified as safe and not addictive by the World Health Organization (WHO) in 2017. CBD is often used in the treatment of insomnia and various chronic pains. Also, the range of proved medicinal positive effects and clinical treatments is growing. **Aim:** With the increasing interest in cannabis and the associated diverse legal requirements, reliable analysis methods are becoming more and more important to determine the efficacy and cannabinoid profiles and thus ensure transparency, homogeneity, and quality during production. The main residues of CBD and cannabigerol (CBG) can be hardly differentiated and separated by standard methods and in order to overcome this challenge an in-house method was developed by Interlabor Belp AG. **Methods:** Our in-house method for analyzing cannabinoids enables the detection of up to 14 cannabinoids in total (Table 1). A unique feature of the enhanced method is its ability to precisely analyze the major impurity of CBD, namely CBG. Our analysis method is based on a chromatographic separation using liquid chromatography, supplemented by precise UV detection. **Results:** With a sensitivity of up to 0.01% (matrix-dependent, generally covered up to 0.1%), our method provides a reliable precision in cannabinoid detection. This ensures compliance with the current legal requirements for THC content in various countries such as Switzerland (THC content < 1%) and Germany (THC content < 0.2%). Compliance with ISO and GMP standards can be assured after a successful matrix-specific validation. **Conclusions:** Interlabor Belp has developed an in-house method for analyses of Cannabis plants, extracts, oils, CBD isolates, capsules, or other products. In-process control in the production of extracts can be challenging, as herbal products can vary in content more than products from conventional production and therefore need to be checked more frequently. **Keywords:** Cannabinoids, analysis, residues, cannabigerol.

Table 1. Overview of Cannabinoids

Cannabinoid	Abbreviation	CAS-Number
Cannabichromene	CBC	20675-51-8
Cannabichromenic acid	CBCA	185505-15-1
Cannabidiol	CBD	13956-29-1
Cannabidiolic acid	CBDA	1244-58-2
Cannabidivarin	CBDV	24274-48-4
Cannabidivarinic acid	CBDVA	31932-13-5
Cannabigerol	CBG	25654-31-3
Cannabigerolic acid	CBGA	25555-57-1
Cannabinol	CBN	521-35-7
Tetrahydrocannabidivarin	THCV	31262-37-0
Tetrahydrocannabivarinic acid	THCVA	39986-26-0
Tetrahydrocannabinolic acid	THCA	23978-85-0
Δ8-Tetrahydrocannabinol	Δ8-THC	5957-75-5
Δ9-Tetrahydrocannabinol	Δ9-THC	1972-08-3

P-16

In Vivo Effects of Novel Allosteric and Dualsteric Cannabinoid Receptor 1 Compounds in Alcohol Use Disorder

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Introduction: Endogenous and synthetic allosteric modulators of cannabinoid receptor 1 (CB_1R) show promise in treating addictive disorders. Novel pharmacological tools to explore allosteric mechanisms can enhance understanding of CB_1R functional selectivity, aiding the development of safer, more effective therapies. **Aims:** We designed, synthesized, and evaluated novel four-arm diarylpyrazoline compounds and CB_1R endogenous peptide derivatives in the *in vitro* and *in vivo* assays. **Methods:** Selective and potent compounds for CB_1R with allosteric potential and/or bitopic nature were screened. Pharmacokinetics (PK), and tissue distributions were assessed by LC-MS/MS after i.p. and oral administration in C57BL6/J mice. *In vivo* CB_1R antagonism efficacy was evaluated through an upper gastrointestinal (GI) motility assay in mice, while anxiogenic activities were assessed using an ambulatory activity assay. Compounds were characterized in the tetrad assay. *In vivo* efficacy in alcohol drinking behavior was tested using the drinking in the dark (DID) and two bottle choice experimental paradigm. **Results:** Novel compounds with high affinity and selectivity for CB_1R in the sub- and low-nanomolar range were tested in functional assays using [^{35}S]-GTPγS binding. The compounds retained high potency for CB_1R antagonism. Six synthetic compounds behaved as non-competitive CB_1R antagonist in GTPγS binding with Schild plot analysis indicating negative allosterism. In PK studies, non-competitive antagonists provided good systemic exposures with C_{max} at 200-300 nM using 3 mg/kg i.p. injections. Acute treatments with enantiomerically pure compounds at 3 mg/kg dose provided maximum *in vivo* efficacy for CB_1R antagonism, fully attenuating CB_1R agonist effect in upper GI motility assay. MRI-2265 was peripherally restricted with 8% brain/plasma ratio, while MRI-2479 was moderately brain penetrant with 34% brain/plasma ratio. Unlike rimonabant (10 mg/kg), neither compound (10 mg/kg) induced hyperambulatory activity. Both compounds reduced alcohol drinking in the DID paradigm in a dose-dependent manner (1, 3, 10 mg/kg). **Conclusions:** We developed peripherally restricted or moderately brain-penetrant bitopic modulators that effectively inhibit CB_1R function, exhibiting favorable pharmacokinetics and potent *in vivo* efficacy without anxiogenic effects. Future studies are needed to further characterize these compounds and endogenous peptide analogs across diverse experimental models and behavioral paradigms to confirm *in vivo* functional selectivity and enhanced CNS safety. **Keywords:** Novel CB_1R allosteric/bitopic modulators, in vivo efficacy.

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P-17

Exploring Non-psychotropic *Cannabis sativa* Extracts for Intestinal Inflammation: An *In Vitro* Approach

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Introduction: *Cannabis sativa* L. is often used by individuals with inflammatory bowel disease to reduce abdominal pain [1], although robust clinical data are limited. Non-psychotropic cannabinoids, e.g. cannabidiol (CBD) and cannabigerol (CBG), are hypothesized to contribute to the anti-inflammatory potential of cannabis [2, 3], yet their effectiveness and safety warrant deeper investigation. **Aims:** This study aimed to evaluate the anti-inflammatory properties of two *C. sativa* extracts obtained through two different extraction methods, with low Δ^9-THC, but standardized in both CBD and CBG, in an *in vitro* model of intestinal inflammation. **Methods:** Human colonocytes (undifferentiated CaCo-2 cells) and enterocytes (differentiated CaCo-2) were stimulated with pro-inflammatory cytokines (IL-1β/IFN-γ), alone or in co-culture with human macrophages (THP-1). The effects of cannabis extracts or individual cannabinoids on key inflammatory mediators (e.g., CXCL-9, CXCL-10, CCL-20) were assessed by ELISA and PCR array. Integrity of the epithelial barrier was evaluated by TEER measurements and ZO-1 immunofluorescence during co-culture with LPS/IFN-γ-stimulated THP-1 cells. **Results:** LC-MS analysis revealed that Extract A and Extract B contained 3.7% *vs.* 4.2% of CBD and 3.1% *vs.* 3.7% of CBG, respectively, with minimal changes observed after *in vitro* digestion. At 100 μg/mL, both extracts suppressed chemokine release and NF-κB activity in colonocytes, matching or surpassing the performance of pure CBD and CBG at 8 μM. Cannabis extracts, particularly Extract B, restored epithelial barrier integrity in co-culture setting, as indicated by improved TEER values and normalized ZO-1 expression (Fig. 1). In contrast, the individual cannabinoids alone did not recover barrier function. These data suggest additional, synergistic components within the extracts may enhance their protective action. **Conclusions:** Standardized *Cannabis sativa* extracts containing CBD and CBG appear to effectively attenuate key inflammatory pathways and preserve epithelial barrier function *in vitro* better than individual cannabinoids. These findings provide a rationale for further research exploring non-psychotropic cannabis extracts as potential therapeutic tools for intestinal inflammation. **Keywords:** Cannabis, intestinal inflammation, CBD, CBG, epithelial barrier. **Acknowledgements:** We gratefully acknowledge Linnea SA (Riazzino, Switzerland) for providing extracts and financial support.

References:

[1] Naftali T et al. J Crohns Colitis 2021; 15(12): 1799-1806.
[2] Schicho R et al. Pharmacology 2012; 89(3-4): 149-155.
[3] Borrelli F et al. Biochem Pharmacol 2013; 85(9): 1306-1316.

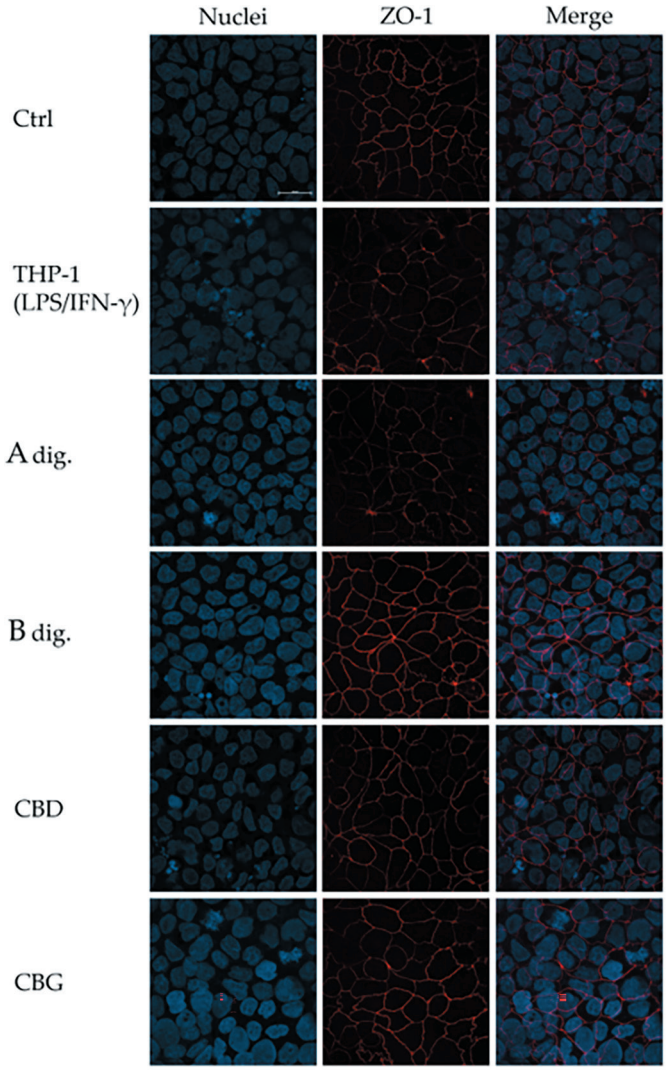

Figure 1. Immunofluorescence images of ZO-1 expression in differentiated CaCo-2 cells co-cultured with stimulated THP-1 and treated for 48 h with either digested Cannabis extracts (A Dig., B Dig.; 100 µg/mL) or pure cannabinoids (CBD, CBG; 8 µM). 60x (scale bar: 20 µm).

P-18

Variability of Cannabinoid Content in Indoor-Grown Cannabis Flowers

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Introduction: The new monograph on cannabis flowers, published in the Ph. Eur. Supplement 11.5 in January 2024, highlights its growing recognition as a promising therapeutic agent for various indications. These include chronic pain, spasticity caused by neurological disorders, like multiple sclerosis, and chemotherapy-induced nausea. While its medicinal potential, particularly associated to the content of Δ^9-tetrahydrocannabinol (THC), is increasingly recognized, achieving consistent treatment outcomes is complicated by the variability in its chemical composition in cannabis flowers. A primary concern is the potential discrepancy between reported and actual THC content, combined with substantial variability among different cannabis flowers, which undermines the reliability of spot-check analyses [1]. **Aim:** To analyze the variability in cannabinoid content and composition in indoor-grown *Cannabis sativa* L. flowers, both among different plants grown from seeds of the same strain/chemovar and across various positions within a single inflorescence. **Methods:** Metamount AG cultivated cannabis flowers from the strains «La S.A.G.E», «Strawberry Glue», «Stracciatella», and «Banana Krushed» under controlled indoor conditions. Flowers were harvested from various plants and different heights on each plant, then dried and extracted following Ph. Helv. 12. The cannabinoid content of these extracts was quantified with a validated electrospray ionization tandem mass spectrometry multiple reaction monitoring (MRM) method using ultra-performance liquid chromatography (UPLC-ESI-MS/MS), allowing for the measurement of the concentrations of more than 20 cannabinoids. **Results:** The THC acid (THCA) content of non-decarboxylated flowers varied dramatically by up to 25% between flowers from different plants under identical environmental conditions. Intriguingly, the THCA content in flowers from the inflorescence apex of the same plant was up to three times higher than in the lateral cola closer to the stem. This effect varied significantly across different cannabis strains. **Conclusion:** Due to the considerable variability in THCA content across different cannabis flowers, the use of medical cannabis should be discussed based on the actual values of each inflorescence, rather than the estimated values based on random sampling. Alternative standardized cannabis API formulations, such as homogeneous powders or extracts, allow for better standardization and more accurate THC delivery to patients, thereby mitigating concerns about inaccurate THC declarations.

Keywords: Tetrahydrocannabinolic acid, chemotype, *Cannabis sativa* L., indoor-growing, MRM.

Reference:

[1] Schwabe AL, Johnson V, Harrelson J, McGlaughlin ME. Uncomfortably high: Testing reveals inflated THC potency on retail Cannabis labels. PLoS One 2023; Apr 12;18(4): e0282396. doi: 10.1371/journal.pone.0282396.

P-19

Exploring the Potential of THC/THCV Cannabis Strains in Preclinical Assays

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Introduction: Medical cannabis has gained recognition as an effective adjunct therapy in palliative care, particularly for chronic pain management. The development of opioid tolerance has highlighted the need for alternative treatments, making medical cannabis an important option. Delta-9-tetrahydrocannabinol (THC) is valued for its analgesic properties but is associated with side effects such as cognitive impairment and sedation. Tetrahydrocannabivarin (THCV) may mitigate these side effects by modulating THC's psychoactive impact while preserving its pain-relieving properties. **Aim:** This study investigates the potential of a cannabis strain combining THC and THCV to maintain pain relief while minimizing adverse effects. **Methods:** *Cannabis sativa* L. strains with elevated THCV levels were screened and cultivated ((AB)-8/5-BetmG - 2022 / 017392). To quantify the activity of CB1 receptors, which are known to mediate THC-induced adverse effects, GRAB_eCB2.0 biosensor was employed [1]. To assess CB2 receptor activity, which has been implicated in the attenuation of inflammatory and neuropathic pain [2], we engineered a CB2-targeted biosensor utilizing a comparable mechanism to the previously described CB1-biosensor. HEK293 cells were transiently transfected with a plasmid encoding the biosensor. Upon subsequent addition of THC and THCV in different ratios, real-time fluorescence measurements were acquired using FLIPR Tetra. Ethanolic extracts were prepared, dried and resuspended in vehicle and tested using a tetrad assay in female C57BL/6 mice. The THC:THCV ratios varied between 1:0.6 and 1:1.9, with a control group receiving artificially added THCV (75 mg/kg). All treatments were administered orally (gavage), and the effects were evaluated 2 h after administration. **Results:** The cannabinoid composition in flowers from the same plants changed over time, with THCV content increasing more significantly relative to THC and 20 other cannabinoids. In comparison to THC alone, the addition of THCV significantly reduced CB1 activity *in vitro*. Furthermore, THCV decreased catalepsy and enhanced locomotion *in vivo*, without compromising the analgesic effects of THC. **Conclusion:** Cannabis strains with balanced THC and THCV levels show promise for effective pain relief with a reduced side effect profile. These results pave the way for an in-human study to validate cannabinoids with high THCV content as alternative analgesics for patients suffering from chronic pain.

Keywords: Tetrahydrocannabinol, tetrahydrocannabivarin, biosensor, tetrad test, analgesia.

References:

[1] Dong A, He K, Dudok B, Farrell JS, Guan W, Liput DJ, Puhl HL, Cai R, Wang H, Duan J, Albarran E, Ding J, Lovinger DM, Li B, Soltesz I, Li Y. A fluorescent sensor for spatiotemporally resolved imaging of endocannabinoid dynamics in vivo. Nat Biotechnol 2022; May; 40(5): 787-798. doi: 10.1038/s41587-021-01074-4

[2] Guindon J, Hohmann AG. Cannabinoid CB2 receptors: a therapeutic target for the treatment of inflammatory and neuropathic pain. Br J Pharmacol 2008; Jan; 153(2): 319-34. doi: 10.1038/sj.bjp.0707531

P-20

Biotransformation of Cannabidiol by *Cannabis sativa* - Derived Endophytes: Unlocking Novel Cannabinoid Potential

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Introduction: In recent years, the exploration of ecological relationships and the ability of endophytic fungi to produce or transform bioactive compounds has driven researchers to investigate their presence in medicinal plants, including cannabis. In this context, a preliminary study was conducted on the endophytic fungi associated with hemp. Twenty-six strains were isolated from various parts of the hemp cultivar «Carmagnola», including leaves, shoots, flower bracts, and fruits, cultivated in Greece. **Methods:** All strains were identified and found to belong to *Chaetomium spp*, *Parachaetomium spp*, *Dichotomopilus spp*, *Aspergillus spp*, *Microascus spp*, *Eremothecium spp*, *Beauveria spp* and *Arthrinium spp*. Ten of the isolated strains were screened for cannabinoid production and were further used in biotransformation experiments of cannabidiol (CBD), which had been previously isolated from the host plant. None of the strains produced CBD. Two strains belonging to species of the family Chaetomiaceae showed interesting chemical biotransformation profiles of CBD and were subjected to large-scale liquid cultures to isolate its biotransformation products. The compounds contained in the ethyl acetate extracts of the cultures were isolated by column chromatography (CC) and semi-preparative high-pressure liquid chromatography (HPLC) and characterized by one- and two-dimensional nuclear magnetic resonance spectoscopy (1 & 2D NMR) and mass spectrometry (MS). **Results:** Among the compounds, 7 new natural products were isolated: a hydroxylated glycosidic derivative of CBD, 5 compounds belonging to the cannabielsoin-type of cannabinoids and a hydroxylated metabolite of cannabidiolaldehyde. Four metabolites showed notable displacement of the labelled synthetic agonist [3H]CP55,940 at CB_2 receptors (IC_{50} 2 to 10 μM), while 6 metabolites showed notable displacement of the labelled synthetic agonist [3H]CP55,940 at CB_1 receptors (IC_{50} 0.5 to 5.08 μM).

Conclusion: These findings highlight the untapped potential of cannabis-associated endophytic fungi as biocatalysts for the transformation of cannabinoids, offering a promising avenue for the discovery of novel bioactive compounds with selective activity at CB1 and CB2 receptors, and paving the way for future research into their therapeutic applications. **Keywords:** Biotransformation, cannabinoids, endophytes, *Cannabis sativa.*

References:

[1] Popp JR, Petrakis EA, Angelis A, Halabalaki M, Bonn GK, Stuppner H, Skaltsounis LA. Rapid Isolation of Acidic Cannabinoids from *Cannabis Sativa* L. Using PH-Zone-Refining Centrifugal Partition Chromatography. J Chromatogr A 2019; 1599: 196-20. https://doi.org/10.1016/j.chroma.2019.04.048.

[2] Tzimas PS, Petrakis EA, Halabalaki M, Skaltsounis LA. Effective Determination of the Principal Non-Psychoactive Cannabinoids in Fiber-Type *Cannabis Sativa* L. by UPLC-PDA Following a Comprehensive Design and Optimization of Extraction Methodology. Anal Chim Acta 2021; 1150: 338200. https://doi.org/10.1016/j.aca.2021.338200.

P-21

Structured Pathways for the Isolation of Bioactive Cannabinoids and Terpenes: From Laboratory to Pilot Scale

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Introduction: The extraction and isolation of bioactive compounds from *Cannabis sativa* are crucial for their therapeutic and commercial applications. This study outlines structured experimental pathways to enhance the efficiency of compounds isolation while ensuring scalability and high purity. **Aims:** To develop and optimize efficient production methodologies for the isolation of cannabidiol (CBD) and minor cannabinoids, such as cannabidivarin (CBDV), cannabichromene (CBC), cannabicitran (CBCT), alongside terpenoids like α-bisabolol, using scalable techniques. **Methods:** Pathway A employs preparative chromatographic methods, including Centrifugal Partition Chromatography (CPC) [1], Medium Pressure Liquid Chromatography (MPLC) and Preparative High-Performance Liquid Chromatography (prep-HPLC), to fractionate and purify cannabinoids. Pathway B employs the use of Short-Path Distillation (SPD) for efficient separation of cannabinoids and terpenes, maximizing CBD production. Analytical characterization of fractions and isolates was conducted using Ultra-Performance Liquid Chromatography-Photodiode Array Detection (UPLC-PDA) [2], Gas Chromatography-Mass Spectrometry (GC-MS), and Nuclear Magnetic Resonance (NMR) spectroscopy. **Results:** Pathway A achieved isolation of CBD and minor cannabinoids like CBDV, CBC, CBCT, and terpenoids like α-bisabolol. Pathway B demonstrated superior scalability, enabling recovery of fractions highly enriched in CBD or terpenes, in a solvent-free process. **Conclusions:** This research highlights the potential of structured methodologies to bridge laboratory precision with industrial scalability for cannabis bioactives. By refining fractionation and isolation processes, these pathways provide a robust framework for cannabinoid-based product development and therapeutic applications. **Keywords:** Cannabidiol, cannabinoid isolation, chromatographic techniques, short-path distillation.

P-22

«To Coagulate, or Not to Coagulate» - That is the Pre-analytical Question for the Quantification of Endocannabinoids in Blood Matrices

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Introduction: The effects of cannabinoids can vary depending on the state of the patient's endocannabinoid system (ECS). A key approach to evaluate the ECS in humans involves quantifying endocannabinoids in biological fluids [1]. The endocannabinoids anandamide (AEA) and 2-arachidonoylglycerol (2-AG) in human blood matrices, primarily plasma and serum, are explored as potential biomarkers for various pathophysiological conditions and may serve as readouts for evaluating novel drugs targeting the ECS. Previous studies suggest that variations in pre-analytical blood processing can affect endocannabinoid levels in blood matrices [2, 3]. **Aims:** A systematic analysis was conducted to evaluate the effects of coagulation, prolonged incubation, and elevated temperatures on endocannabinoid levels in serum, plasma, and whole blood cells. **Methods:** Human blood was collected in EDTA and coagulation tubes and incubated for various time periods using different temperatures. After centrifugation plasma, serum and blood cells were collected. Endocannabinoids and ECS related lipids were quantified by liquid chromatography-electrospray ionization-tandem mass spectrometry. **Results:** 2-AG was increased in coagulated blood cells and serum compared to non-coagulated blood cells and plasma. 30 min of coagulation were sufficient to strongly increase 2-AG and associated lipids in blood cells. While a higher coagulation temperature (37 °C compared to 22 °C) did not impact 2-AG levels in blood cells, it strongly enhanced the release of 2-AG into the serum. In contrast, the coagulation did not impact AEA and structurally related *N*-acylethanolamines, which were increased in plasma, serum and blood cells with prolonged blood incubation time (1 h). A higher coagulation temperature further increased AEA in blood cells, but not in serum. **Conclusions:** Coagulation significantly affects 2-AG and ECS-related lipid levels in serum and blood cells, with temperature playing a key role. Higher coagulation temperatures amplify 2-AG release into serum, while AEA levels increase mainly with prolonged incubation of blood samples. A strict control of sample handling, including rapid cooling and minimizing pre-centrifugation time, is crucial to reduce variability caused by pre-analytical sample processing. Therefore, plasma or

whole blood are the preferable matrices for the analysis of circulating endocannabinoids. Notably, 2-AG released during coagulation warrants further investigations as a potential biomarker for specific pathologies. **Keywords:** Endocannabinoids, endocannabinoid system, coagulation, serum, plasma.

References:

[1] Meier P et al. Comparative targeted lipidomics between serum and cerebrospinal fluid of multiple sclerosis patients shows sex and age-specific differences of endocannabinoids and glucocorticoids. Acta Neuropathol Commun 2024; 12: 160.
[2] Kratz D et al. Pre-analytical challenges for the quantification of endocannabinoids in human serum. J Chromatogr B Analyt Technol Biomed Life Sci 2022; 1190: 123102.
[3] Kratz D, Thomas D, Gurke R. Endocannabinoids as potential biomarkers: It's all about pre-analytics. J Mass Spectrom Adv Clin Lab 2021; 22: 56-63.

P-23

Holistic and Safe Approach to Medical Cannabis in Elderly Care: Insights from Israel and Germany

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Introduction: The global geriatric population is growing rapidly, surpassing the active workforce and challenging healthcare systems with increased costs and impacts on seniors' quality of life. Polypharmacy raises severe adverse effect risks, leading to mortality. In the U.S., up to 35% of elderly community patients and 40% of hospitalized elderly experience adverse drug reactions [1]. In Germany, patients aged ≥ 80 years use an average of 6.2 drugs per person, raising drug-related adverse event risks [2]. Antipsychotics, commonly prescribed for dementia, exacerbate risks. Designed for psychiatric use, they are often unsuitable for the elderly, leading to poor outcomes. The U.S. FDA issued a «black box warning» for antipsychotics due to increased mortality in elderly dementia patients. Conversely, medical cannabis offers a safer alternative, improving calm, appetite, sleep, and overall quality of life [3]. **Aims:** (1) Highlight the LEEMA approach's role in improving geriatric quality of life; (2) compare cannabis types, delivery methods, and production processes in Israel and Germany; (3) showcase the impact of medication reduction and multidisciplinary team support. **Methods:** The LEEMA approach combines comprehensive geriatric assessments, personalized cannabis treatment, titration monitoring, patient education, risk management, and multidisciplinary team collaboration. **Results:** Patients in Israel and Germany showed significant improvements in sleep, appetite, and behavioral symptoms. The approach enabled safe medication reduction and improved quality of life while minimizing adverse effects. Comparative insights highlighted unique aspects of care in each country, including different cannabis types and formulations. **Conclusions:** The LEEMA approach offers a scalable model for treating both hospitalized and home-based patients. It improves the quality of life for geriatric patients with an emphasis on safety, efficacy, and tailored care. **Keywords:** Medical cannabis, geriatric care, polypharmacy, dementia treatment, personalized medicine.

References:

[1] American College of Osteopathic Family Physicians. Polypharmacy in the Elderly. Accessed from [https://www.acofp.org].
[2] Klarin I, Wimo A, Fastbom J. The association of inappropriate drug use with hospitalisation and mortality: a population-based study of the very old. BMC Geriatrics. 2020; 20: 143. doi: 10.1186/s12877-020-1430-6.
[3] Sikorin I, Abuhasira R, Shbiro L. Medical Cannabis for Older Patients-Treatment Protocol and Initial Results. J Clin Med 2019; 8(11): 1819. doi: 10.3390/jcm8111819.

P-24

Extraction, Metabolite Profiling and Assessment of the Antiproliferative Activity on Glioblastoma Multiforme Cancer Cells of Cannabinoids from Non-psychoactive *Cannabis sativa* L.

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Introduction: Glioblastoma multiforme (GBM) is one of the most frequent malignant and lethal forms of brain cancer. It is characterized by a high rate of proliferation, invasion, angiogenesis and resistance to standard anticancer therapies. Many studies have highlighted the potential antiproliferative effects of cannabinoids, terpenophenolic compounds derived from *Cannabis sativa* L., on various cancer types. Among non-psychoactive cannabinoids, cannabidiol (CBD) is able to reduce cancer cell proliferation and to induce apoptosis [1]. Furthermore, since CBD can cross the blood-brain barrier (BBB), it is believed to exert an antiproliferative effect on central nervous system (CNS) cancers, including GBM. **Aims:** The aim of this study was to investigate the antiproliferative activity of a cannabinoid-enriched fraction (CEF), extracted and entirely characterized from the inflorescences of non-psychotropic *C. sativa*, and to evaluate its bioactivity *in vitro* against GBM cancer cell lines (U87 and T98G). **Methods:** The composition of the CEF was carried out through targeted metabolomics using UHPLC-HRMS for qualitative assessment, with CBD as the predominant compound confirmed by quantitative analysis performed with HPLC-UV [2]. **Results:** Cell viability was evaluated after 24 and 48 h of exposure to CEF and CBD in U87 and T98G human GBM cancer cell lines, with temozolomide (TMZ) used as the positive control. The results indicated that CEF and CBD treatments produced comparable results on cell viability inhibition in both cancer cell lines in a time and dose-dependent manner. **Conclusions:** Further studies are currently on-going to disclose mechanism/s of action of CEF and CBD against GBM using both omics techniques and functional bioassays. **Keywords:** Glioblastoma multiforme, non-psychoactive cannabinoids, cannabidiol, *Cannabis sativa* L. **Acknowledgements:** The

project was financed by the European Union - Next Generation EU «Targeting microglia CB2 Receptors with novel multisite ligands: a multidisciplinary and translational study for the identification of an innovative multiple sclerosis therapy» (2022BNSNS2, CUP E53D23012360006).

References:

[1] Anceschi L et al. Chemical characterization of non-psychoactive *Cannabis sativa* L. extracts, in vitro antiproliferative activity and induction of apoptosis in chronic myelogenous leukaemia cancer cells. Phytotherapy Res 2022; 36(2): 914-927 https://doi.org/10.1002/ptr.7357
[2] Durante C et al. Application of experimental design in HPLC method optimisation for the simultaneous determination of multiple bioactive cannabinoids. J Pharm Biomed Anal (2022; 221: 115037. https://doi.org/10.1016/j.jpba.2022.115037

P-25

A Case of Treatment with Medicinal Cannabis for Orofacial Pain

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Introduction: Chronic refractory pain (COP) is pain that does not improve with conventional treatments and can cause a lot of suffering to the patient, is a medical condition characterized by pain that persists for months. It can be caused by a variety of conditions, such as neurological, infectious, autoimmune diseases, among others. These conditions represent a clinical challenge, as they are difficult to manage therapeutically, and COP disorders in general represent a major health problem due to their impact on quality of life. Several medications have been used to treat orofacial pain, which end up causing adverse reactions as well as side effects. New therapies have been studied, such as the applicability of medicinal cannabis. **Aims:** To present a clinical case of the use of cannabis proving its positive action in orofacial pain, bring back physical, emotional, and cognitive balance alleviating stress and anxiety, based on scientific articles. **Methods:** A 40-years old female patient came to consultation with a complaint of COP and was being treated for orofacial pain. She reported facial pain, swelling, migraines, cervical pain, clicking and ear pain, difficulty opening her mouth, teeth grinding sounds at night, as well as routine clenching of her teeth, insomnia, anxiety and depression. This patient had already been seen by 3 different specialists: neurologist, otorhinolaryngologist and ophthalmologist. The patient was diagnosed with temporomandibular dysfunction (TMD) and advanced bruxism. The patient was taking conventional medications, such as antidepressants, benzodiazepines and anticonvulsants, but continued to feel pain and thus had limitations in her life quality. Start of medication with full spectrum cannabis oil 1500 mg in March 2021. **Results:** In July 2021, with 0.5 mL of cannabis oil 3 times per day, the patient was happy, willing, without headaches, swelling, jaw popping, or neck pain. At the end of the treatment in November 2021, the patient had weaned off all allopathic medication. **Conclusion**: Analgesia is one of the main therapeutic targets of medicinal cannabis in the treatment of symptoms associated with COP. In addition to reducing spasticity, anxiolytic effects, muscle relaxation and anti-inflammatory effects were observed due to the reduction in the release of pro-inflammatory cytokines. **Keywords:** Cannabis, orofacial pain, TMD, bruxism.

References:

[1] Nitecka-Buchta A et al. Myorelaxant Effect of Transdermal Cannabidiol Application in Patients with TMD: A Randomized, Double-Blind Trial. J Clin Med 2019; Nov 6; 8(11): 1886. doi: 10.3390/jcm8111886
[2] Longworth J et al. Cannabis and cannabinoid medications for the treatment of chronic orofacial pain: A scoping review. Dentistry Review 2023; 3(1): 100063
[3] Pina-Escudero SD et al. Cannabidiol in the management of bruxism in behavioral variant of frontotemporal degeneration. Neurocase 2021; 27(2): 209–211. https://doi.org/10.1080/13554794.2021.1917620

P-26

Low-dose Cannabidiol Treatment Prevents Chronic Stress-induced Sequelae and is Associated with Multiple Synaptic Changes Across Various Brain Regions

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Introduction: Major Depressive Disorder (MDD) is a heterogeneous and debilitating mood disorder often associated with stress. Although current treatments are available, they remain ineffective for approximately 30% of affected individuals and are frequently accompanied by undesirable side effects. Cannabidiol (CBD) has emerged as a potential and safe therapeutic option for alleviating depressive symptoms. **Aims:** Here we sought to deepen the underlying molecular mechanisms through which this compound exerts its beneficial effects using a very low dose. **Methods:** We performed a chronic stress (CUMS) protocol to induce depressive-like sequelae evaluated by subjecting the experimental mice to several behavioral tests. Second, we employed mass spectrometry (MS) in different brain regions to explore the molecular pathways altered by the lowest dose of CBD in the CUMS protocol. We utilized advanced confocal microscopy to study the microstructural synaptic changes mediated by the CBD low dose. **Results:** In this study, we demonstrate that a very low dose of CBD (1 mg/kg) can effectively reverse various sequelae induced by chronic stress, a well-established mouse model used to simulate depressive-like symptoms. MS revealed several molecular improvements following CBD treatment, particularly in the medial prefrontal cortex (mPFC), across multiple neurotransmission systems (including glutamatergic and serotonergic pathways). Microstructural experiments, utilizing double-labeling of F-Actin and VGlut1-positive clusters, revealed a complete restoration of

mature synapses in the mPFC of mice treated with CBD. **Conclusions:** Our findings indicate that a very low dose of CBD is effective in counteracting the adverse effects of chronic stress, possibly through the synaptic remodeling of excitatory synapses in the mPFC. **Keywords:** Cannabidiol, mice, Major Depressive Disorder, chronic stress protocol, MS. **Acknowledgements:** This study has been sponsored by Schibano Swiss Pharma.

P-27

«Weed ain't What it Was»: Chemotypic Dynamics of Cannabis Categories

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Introduction: No plant is broader in its uses than *Cannabis sativa*. This is reflected in the broad geno-, pheno- and chemotypic diversity of traditional cultivars. Drug-type cannabis is differentiated by categorisation into «sativa» and «indica», with traditional cultivars divided and considered representative accessions of each class in its pure state. Relative homogeneity between «sativas» and «indicas» is fuelling a movement to replace the current system of nomenclature with one based around chemovars with distinct and consistent phytochemical profiles. **Aims:** To investigate the chemotypic ranges of traditional, classic and contemporary cannabis categories and evaluate the chemotypic validity of these categories and accuracy of these narratives. **Methods:** This paper performs a quantitative meta-analysis over 6 cannabinoids and 20 terpenoids to compare the chemotypic ranges of these categories from three modern eras of drug-type cannabis. **Results:** We find that classic «sativas» and «indicas» diverged from the chemotypic ranges of their reported ancestors, i.e. tropical ganja cultivars and Central Asian charas cultivars. Then these categories converged to the «relatively homogeneous» [1] cannabis that dominates the commercial markets in the USA. **Conclusions:** Tropical ganja and Central Asian charas cultivars are described as «pure sativas» and «pure indicas», respectively, yet they possess distinct chemotypic ranges. We recognise the chemotypic validity of these traditional categories and classic «Dutch Sativas» and «Indicas». We address the need to separate the distinct traditional categories and the relatively homogeneous cannabis in the contemporary American market from the «sativa/indica» narrative and for preserving both traditional and classic germplasm in the face of increasing homogeneity. **Keywords:** Chemotype, chemotaxonomy, taxonomy, landraces, chemovar.

Reference:

[1] Smith CJ et al. The phytochemical diversity of commercial Cannabis in the United States. PloS one 2022; 17.5: e0267498.

P-28

CYP450 Interactions of THC and CBD with Medications: A Comparative Analysis

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Introduction: Delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) can alter drug metabolism of medications that share CYP450 pathways. Three *in vitro* studies [1-3] evaluated these interactions with differing results. All three reported CYP2C9 inhibition by THC and CYP2C9 and CYP2C19 inhibition by CBD. Nasrin and Bansal [1, 2] identified CYP1A2 inhibition by THC and CYP1A2 and CYP2D6 inhibition by CBD, while Doohan [3] did not. Nasrin and Doohan reported CYP2B6 inhibition by CBD, but Bansal did not. Bansal and Doohan observed CYP3A4 inhibition by CBD, which Nasrin did not. **Aims:** To describe differences in «potential» CYP450 interactions between THC, CBD and medications in our participant panel, based on the three key *in vitro* studies [1-3]. **Methods:** Participants from a larger cohort who reported oral cannabis use were identified, clinical notes manually reviewed to confirm cannabis use, and medication lists closest cannabis documentation were abstracted. Two pharmacists identified and categorized interactions by the CYP450 reported in the 3 studies. **Results:** We identified 71 participants with oral cannabis use, averaging 68.5 years old. The sample was predominantly women (73.2%), Caucasian (94.4%), and non-Hispanic (95.8%). Potential CYP450 interactions for THC and CBD with medications varied across the 3 studies.THC interactions were 119 [1], 166 [2], and 20 [3]. For CBD, interactions were 247 [1], 243 [2], and 175 [3]. **Conclusions:** The variability in CYP450 interactions between THC, CBD, and medications depending on the study underscores the need for well-designed *in vivo* studies to direct management of these interactions in clinical practice. **Keywords:** THC, CBD, drug-interactions, CYP450, cannabinoids.

References:

[1] Nasrin S, Watson CJW, Perez-Paramo YX, Lazarus P. Cannabinoid Metabolites as Inhibitors of Major Hepatic CYP450 Enzymes, with Implications for Cannabis-Drug Interactions. Drug Metab Dispos 2021; Dec; 49(12): 1070-1080. doi: 10.1124/dmd.121.000442. Epub 2021 Sep 7. PMID: 34493602; PMCID: PMC11022895.

[2] Bansal S, Zamarripa CA, Spindle TR, Weerts EM, Thummel KE, Vandrey R, Paine MF, Unadkat JD. Evaluation of Cytochrome P450-Mediated Cannabinoid-Drug Interactions in Healthy Adult Participants. Clin Pharmacol Ther 2023; Sep; 114(3): 693-703. doi: 10.1002/cpt.2973. Epub 2023 Jun 30. PMID: 37313955; PMCID: PMC11059946.

[3] Doohan PT, Oldfield LD, Arnold JC, Anderson LL. Cannabinoid Interactions with Cytochrome P450 Drug Metabolism: a Full-Spectrum Characterization. AAPS J 2021; Jun 28; 23(4):91. doi: 10.1208/s12248-021-00616-7. PMID: 34181150.

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Catalytic Synthesis of Cannabinoids

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Introduction: Cannabidiol (CBD) and delta-9-tetrahydrocannabinol (THC) are major components of the cannabis plant, while cannabinol (CBN) is a minor component, which is typically extracted from aged cannabis. There is a growing demand for pure, single component cannabinoids for research and medicinal applications. **Aims:** In order to address the demand for high purity cannabinoid products, we aim to develop catalytic processes for the cost-effective and simple preparation of cannabinoids, including rare cannabinoids. **Methods:** Cannabinoid precursor compounds were prepared and used for the catalytic synthesis of several classes of cannabinoids under mild conditions. The precursors include 3,5-dihydroxy-4-((1R,6R)-3-methyl-6-(prop-1-en-2-yl)cyclohex-2-enyl)phenyl trifluoromethanesulfonate ((R,R)-CBD-OTf), (6aR,10aR)-1-hydroxy-6,6-9-trimethyl-6a,7,8,10a-tetrahydro-6H-benzo-[c]chromen-3-yltrifluoromethanesulfonate((R,R)-THC-OTf) and 1-hydroxy-6,6,9-trimethyl-6H-benzo[c]chromen-3-yl trifluoromethanesulfonate (CBN-OTf). The structures of the precursors are shown in Figure 1 (a). These were used to prepare CBD (and CBD analogues), THC (and THC analogues) and CBN (and CBN analogues) in one or two steps using catalytic coupling reactions, as shown in Figure 1 (b) for the preparation of CBD. **Results:** The cannabinoids were prepared and isolated in high yields and purity. The preparation of related cannabinoid precursors such as (S,S)-CBD-OTf, (R,S)-CBD-OTf, (S,R)-CBD-OTf, (S,S)-THC-OTf, (R,S)-THC-OTf and (S,R)-THC-OTf will be presented, along with their use for the preparation of (S,S)-CBD, (R,S)-CBD, (S,R)-CBD, (S,S)-THC, (R,S)-THC and (S,R)-THC and related cannabinoid analogues. **Conclusions:** Several cannabinoid precursor compounds were prepared and used to prepare a range of CBD-type, THC-type and CBN-type cannabinoids in high yields and purity. The procedures were extended to the preparation of cannabinoids containing deuterium and carbon-13. **Keywords:** Cannabinoids, catalysis, isomers, deuterium, carbon-13.

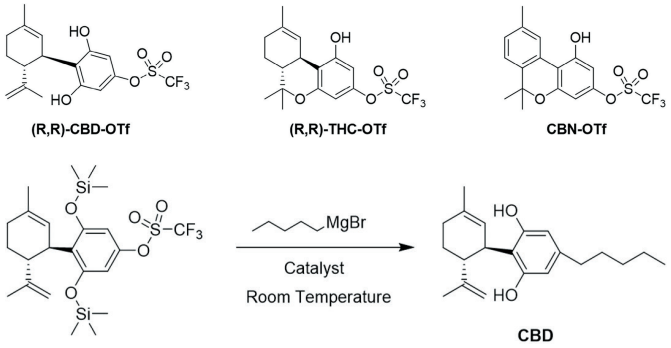

Fig. 1. (a) Cannabinoid precursors **(b)** catalytic preparation of CBD.

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Involving Cannabis Users in the Development of the Intervention of a Trial on Regulated Recreational Cannabis Sale in Pharmacies

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Introduction: Switzerland has taken a globally unique path to cannabis regulation. A 2021 law allows researchers to conduct regulatory experiments on the production and sale of cannabis for non-medical purposes. Our large randomised controlled trial (RCT) aimed to test how selling cannabis in pharmacies affects users' health and consumption habits. Acknowledging the persistent stigma surrounding cannabis use, we sought a way to incorporate cannabis users' perspectives. **Aims:** Our PPI aims were to adapt the study intervention to user needs and to ensure trial acceptability. **Methods:** When planning our RCT, we formed an advisory group with regular cannabis users. We used convenience sampling (including snowball sampling) to recruit participants. A qualitative researcher conducted a first individual Zoom interview, followed by in-person group discussions. She recorded and transcribed the sessions, and then analysed them with qualitative content analysis using a qualitative data analysis software. She summarised the advisory group's feedback in reports, which we used to adapt the study intervention. We assured participants of the anonymisation of their personal data and provided hourly remuneration for their time. **Results:** Between January 2021 and March 2024, 8 cannabis users provided extensive feedback that informed our study intervention. Based on their insights, we expanded the product selection to include cannabis resin alongside cannabis flowers. The group's feedback also led us to make several changes to the sales process in pharmacies. While the members of the advisory group expressed that much of their feedback had been considered, they noted that some key aspects - such as product pricing - had not been implemented. This is partly explained by legal constraints limiting our ability to implement advisory group feedback. **Conclusions:** We found that including cannabis users' perspectives proved to be an effective way to better adapt the study intervention to real-world needs. Our experience showed that gathering user input is feasible, even in highly regulated environments and despite ongoing stigma surrounding cannabis use. **Keywords:** SCRIPT, patient and public involvement, cannabis regulation, advisory group. **Acknowledgements:** Many thanks go to all the people in the advisory group who have dedicated their time to the SCRIPT study over the years.

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Anticholinergic Activity of Cannabinoids from Different Strains: An *In Vitro* and *In Silico* Approach

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Introduction: *Cannabis sativa* is a plant with various strains, each offering unique therapeutic potential due to its diverse cannabinoid content. It demonstrates anti-inflammatory, analgesic, anxiolytic, anticonvulsant, and neuroprotective properties. Among its many biological activities, cannabinoids have been shown to inhibit cholinesterases, enzymes implicated in neurodegenerative diseases like Alzheimer's and Parkinson's disease. **Aims:** The aim of the research was to investigate the relationship between the content of individual cannabinoids in different *Cannabis sativa* strains and various plant organs, as well as their anticholinergic activity, using a combined *in vitro* and *in silico* approach. **Methods:** Plant material was extracted using a supercritical CO_2 extraction process conducted at 6000 PSI and 50°C. The cannabinoid content was analyzed using HPLC-DAD. The potential to inhibit acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) *in vitro* was assessed spectrophotometrically. In the *in silico* analysis, molecular docking was performed using AutoDock Vina version 1.2.0. The best scoring poses were exported to PDBQT format, converted to PDB format using Open Babel, and analyzed with the PLIP server to identify interactions between cannabinoids and the enzyme active sites. The docked complexes were visualized in PyMOL and further evaluated in Prank-Web to generate and assess 3D models of the active sites. **Results:** The ability to inhibit acetylcholinesterase and butyrylcholinesterase varied across different *Cannabis sativa* strains. Inflorescences exhibited a higher anticholinergic potential compared to leaves. The content and composition of various cannabinoids influenced this potential. The domains responsible for this inhibitory activity were identified as the active sites of acetylcholinesterase and butyrylcholinesterase, where cannabinoids interacted through hydrogen bonding, hydrophobic interactions, and π-π stacking, as determined by *in silico* molecular docking and protein-ligand interaction analyses. **Keywords:** Cannabidiol, tetrahydrocannabinol, anticholinergic activity, acetylcholinesterase, neuroprotection. **Acknowledgments:** This research was funded in whole by National Science Centre, Poland, the grant Preludium nr UMO-2021/41/N/NZ7/01125.

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Cultivar Matters: Cannabinoid-independent Entourage Effect

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Introduction: The medical effects of different cannabis cultivars cannot just be explained by the main cannabinoids they contain. However, there is little evidence of other compounds that play an essential role in their medical effects. **Method:** In this study, we used the nematode *C. elegans* as an independent test system to investigate the entourage effect of 12 medicinal cannabis cultivars. The cultivars were selected based on the most diverse effectivity reported by patients. We tested 9 THC-rich and 3 CBD-rich cultivars by exposing the nematodes to different fractions: apolar fractions (high in cannabinoids and terpenes) and polar fractions (low in cannabinoids, relatively high in flavonoids). The assays were chosen based on results of the patient survey highlighting medical effects on appetite, mobility, and nervous system. **Results:** Appetite was measured by exposing *C. elegans* to the 12 different cultivars and subsequently determining the pharyngeal pumping rate, which shows the transport rate of food (bacteria) from the mouth to the intestine and therefore evaluated the amount of food ingested by the nematodes. In Figure 1A, the polar, low-cannabinoid fraction of two cultivars showed significant effects: a THC-rich cultivar (smT7) and a CBD-rich cultivar (smC1). Figure 1B indicates that a THC cultivar with the same cannabinoid profile as smT7 (smT9) showed no effect, nor did smC2, a CBD cultivar with a similar cannabinoid profile to smC1. Figure 1C shows that the apolar fraction (high-cannabinoid fraction) did not impact pharyngeal pumping. This suggests that cannabinoid content is unlikely to be the determining factor in regulating appetite. Instead, the effect seems to be cultivar-specific and regulated by compounds in the polar fraction. These cultivar-specific results were supported by measuring mobility (number of body bends per minute) and nervous system effects (reaction time for a full bend backwards after exposure to an

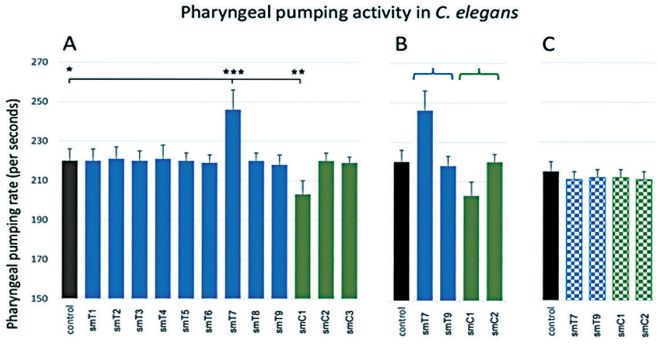

*Figure 1. Effect of different cannabis varieties on pharyngeal pumping activity in C. elegans. Blue bars: extracts obtained from THC-rich varieties; green bars: extracts of obtained CBD rich varieties. (A) overvieuw of all tested cultivars; (B) different effects of two varieties with the same THC content (blue bars) or CBD content (green bars); (C) effects of only pure cannabinoids as present in the tested varieties of (B). *** = false discovery rate (FDR)-corrected p < .001; ** = FDR-corrected p < .01; * = FDR-corrected p < .05*

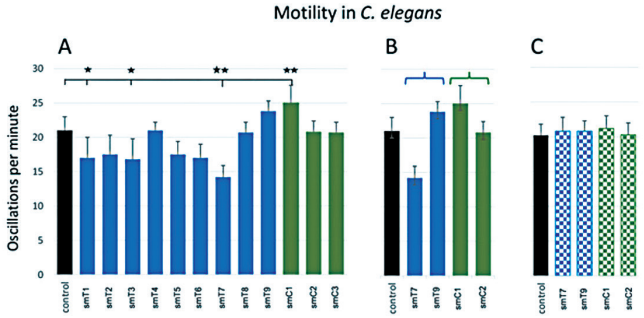

*Figure 2. Effect of different cannabis varieties on moltility in C. elegans. Blue bars: extracts obtained from THC-rich varieties; green bars: extracts of obtained CBD rich varieties. (A) overvieuw of all tested cultivars; (B) different effects of two varieties with the same THC content (blue bars) or CBD content (green bars); (C) effects of only pure cannabinoids as present in the tested varieties of (B). *** = false discovery rate (FDR)-corrected p < .001; ** = FDR -corrected p < .01; * = FDR-corrected p < .05*

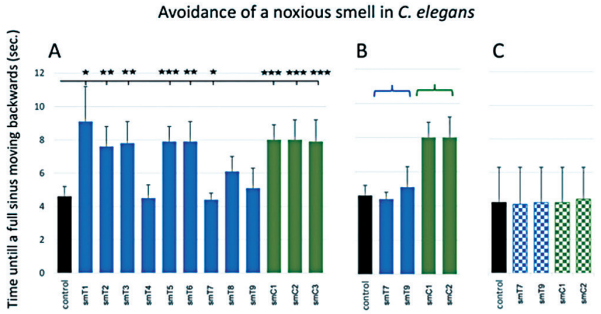

*Figure 3. Effect of different cannabis varieties on the nervous system in C. elegans. Blue bars: extracts obtained from THC-rich varieties; green bars: extracts of obtained CBD rich varieties. (A) overvieuw of all tested cultivars; (B) effects of two varieties with the same THC content (blue bars) or CBD content (green bars); (C) effects of only pure cannabinoids as present in the tested varieties of (B). *** = false discovery rate (FDR)-corrected p < .001; ** = FDR-corrected p < .01; * = FDR-corrected p < .05*

unpleasant odor). Both tests showed effectiveness of the polar, low-cannabinoid fractions of smT7 and smC1 but no effects from the apolar, high-cannabinoid fractions. **Conclusion**: Since cannabis cultivars with similar cannabinoid profiles demonstrate different effects, it is crucial to base research or product development on cultivars with demonstrated efficacy. The polar fractions of smT7 and smC1 show promising results for further development of products targeting weight gain or weight loss/obesity management. **Keywords:** Cannabis cultivars, weight loss management, obesity, polar and apolar fractions, THC, CBD, flavonoids, terpenes, nematode *C.elegans*, appetite, motility, nervous system. **Acknowledgements:** The authors would like to thank Marcel de Wit for all his preparatory work in research and breeding cannabis cultivars with essential medical properties. This study has been published in the Journal of Cannabis Research 2022; 4: 53; https://doi.org/10.1186/s42238-022-00162-9

Medical Cannabis and Cannabinoids

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