

# Medical Cannabis 2024

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**Changes in mTOR Activity and Metabolome May Contribute to the Anti-Ageing Effect of Long-Term  $\Delta$ 9-Tetrahydrocannabinol Treatment****Andras Bilkei-Gorzo<sup>1</sup>***Institut of Molecular Psychiatry, University Clinics Bonn, Germany*

Brain ageing is associated with cognitive decline, reduced synaptic plasticity and altered metabolism. Previous studies with genetically modified animals have shown that the activity of the cannabinoid system has a significant effect on the ageing process. Cannabinoid receptor 1 (CB1) knockout mice showed early onset of cognitive deficits associated with reduced neurogenesis, neuronal loss and increased pro-inflammatory glial activity - typical signs of brain ageing. Consistent with these data, pharmacological studies showed that increasing CB1 receptor activity through chronic  $\Delta$ 9-tetrahydrocannabinol ( $\Delta$ 9-THC) treatment restored several symptoms of brain ageing. Whether changes in mechanistic target of rapamycin (mTOR) signaling and metabolome are associated with its positive effects on the ageing brain was an open question. Information about availability of resources or scarcity is imperative for metabolic regulation in all organisms. In higher organisms, mTOR is a sensitive intracellular energy sensor system, and its activity has a major impact on ageing by regulating cellular metabolism. Reduced mTOR signaling through low calorie diet, intensive physical activity or pharmacological treatment has though a general anti-ageing effect but it can negatively affect the ageing brain by reducing synaptogenesis therefore also cognitive abilities. Thus, anti-aging strategies based on the reduction of mTOR activity could be not only ineffective but even counter-productive against brain ageing. In our present work we now found a strategy to solve this dilemma showing that  $\Delta$ 9-THC treatment has a tissue-dependent and dual effect on mTOR signaling and the metabolome. In the brain,  $\Delta$ 9-THC treatment induced a transient increase in mTOR activity and in the levels of metabolites involved in energy production and amino acids enabling an increased synthesis of synaptic proteins and thus generation of new synapses. Unexpectedly, we found a similar reduction in the mTOR activity in adipose tissue and in the level of amino acids and carbohydrate metabolites in blood plasma as in animals on a low-calorie diet or after intensive physical activities. We concluded that long-term  $\Delta$ 9-THC treatment first has a pro-cognitive effect by increasing energy and synaptic protein production in the brain, followed by an anti-aging effect - reduction in mTOR activity and metabolic processes in the periphery. Our study suggests that a dual effect on mTOR activity and the metabolome could be the basis for an effective anti-aging and pro-cognitive medication.

## **Harnessing the Power of Industrial Hemp: Antioxidant, Neuroprotective, and Prebiotic Applications of Białobrzieszka Extracts**

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**Abstract:** The Białobrzieszka variety of industrial hemp, traditionally grown for its fibre, is increasingly recognised for its rich cannabinoid profile, including CBD, CBG, CBN, THC, and CBC. This study explores the therapeutic potential of cannabinoid-rich extracts from this variety, focusing on their antioxidant, neuroprotective, and prebiotic properties.

**Objectives:** Our research aimed to quantify the cannabinoid content of Białobrzieszka hemp extracts and assess their biological activities, particularly their impact on oxidative stress, neuroprotection, and prebiotic activity.

**Methods:** To maximise yield, cannabinoid-rich extracts were obtained using supercritical fluid extraction (SFE) under optimised conditions. The antioxidant activity of the extracts was evaluated through various in vitro assays, including DPPH and ABTS radical scavenging tests. The neuroprotective potential was assessed by measuring the inhibition of acetylcholinesterase (AChE) and butyrylcholinesterase (BChE), enzymes linked to neurodegenerative conditions. Additionally, the prebiotic potential of the extracts was tested by integrating them into systems containing dextran, inulin, and trehalose, and their effects on the growth of beneficial gut bacteria were assessed.

**Results:** Among the tested extracts, Extract 9, with the highest cannabinoid concentration, demonstrated exceptional antioxidant and neuroprotective activities, significantly inhibiting AChE and BChE. Furthermore, prebiotic systems incorporating these extracts successfully preserved the active compounds and maintained their biological activity, promoting the growth of beneficial gut bacteria.

**Conclusion:** The findings underscore the therapeutic potential of Białobrzieszka hemp extracts, particularly for their antioxidant, neuroprotective, and prebiotic properties. These extracts could serve as promising candidates for functional foods and therapeutic applications. Further studies are needed to refine these formulations and further explore their clinical potential.

Clinical Studies

**A Case of Treatment with Cannabis Medicinal for Orofacial Pain**

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**Introduction:** Neuropathic orofacial pain (NOP) is a chronic pain condition involving the head, face, neck and is associated with dysfunction or primary lesion in the nervous system. These conditions represent a clinical challenge as they are difficult to manage therapeutically and NOP disorders in general represent a major health concern due to their impact on quality of life. Several drugs have been used for the treatment of orofacial pain. Therefore, new therapies have been studied, such as the applicability of Cannabis.

**Objective:** To present a clinical case of the use of Cannabis proving the positive action on orofacial pain.

**Case description:** AD, 50, female came to the first consultation complaining of NOP undergoing treatment for orofacial pain. Reports pain in the nasal region, moving to the right lip with a sensation of numbness. Ear pain as well, with swelling in the face, difficulty opening the mouth, grinding teeth at night and clenching teeth routinely. The patient had diagnoses with Trigeminal Neuralgia due to left paralysis with right symptoms. Patient used conventional drugs, such antidepressant, benzodiazepine, anticonvulsivant however, continue to experience pain with life limiting. Start of medication with Cannabis Oil CBD 25:1 on 04/18/22.

**Discussion:** Analgesia is one the principal therapeutic targets of the Cannabis in the treatment of symptoms associated with NOP.

**Conclusion:** On 08/16/22 with 1 mL of Oil CBD 2x a day and 1/2 THC Gum, the patient was pain free, tingling free and opening her mouth normally. End of Treatment in January 2023 with patient discharge.

Clinical Studies

**Practical Experiences and Perceptions of the Effects of Cannabidiol as an Additional Treatment in Refractory Epilepsy in Children Duma F1\*, Nonkulovski D1, Muaremoska Kanzoska L1 1 University Pediatric Clinic, Clinical Center “Mother Tereza”, Skopje \***

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Abstract

Up to 40% of children with epilepsy will not achieve seizure freedom with antiepileptic drugs (AEDs) Cannabis-based treatments for epilepsy have generated much interest and scientific researches.

Purpose: To describe effects of CBD as additional treatment in refractory epilepsy in 20 children.

Methods: A prospective observation describing the effect of oral oil solution (15 mg CBD + 1 mg THC/ 1 ml as additional treatment in 20 outpatient children (age 3–11 years) with intractable epilepsy resistant to 2 AED and signed informed consent in period July 2017- May 2018.

Observation included assessment of treatment efficacy (number and frequency of seizures) and tolerability (frequency and strength of undesirable effects) by parental diary report.

Results: Effects of treatment were assessed in 18 children. One patient was seizure free. Reduction in seizure frequency ranging (50-80%) was reported for five (~29%) patients, intermittent reduction of seizure frequency was reported for four children (~24%) and for three children (~18%) insignificant change in seizure frequency was reported. Five (~29%) patients withdraw the treatment: two due to nonadherence to treatment, one due to operation procedure and in two patient aggravations of seizures were reported.

No adverse reactions were reported.

Conclusion: CBD treatment is a promising one and further prospective trials are warranted.

Clinical Studies

**Dysmenorrhea - Use of Cannabidiol Intravaginally**

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**Background:** More than 50% in women of reproductive age suffer from menstrual cramps. 80% of dysmenorrhea patients resort to self-medication with painkillers.

**Objectives:** Can vaginal tampons infused with Cannabidiol oil help to alleviate dysmenorrhea when inserted into the vagina?

**Methods:** Between April 2023 and March 2024 thirty women with menstrual cramps of varying severity without hormonal contraception were monitored for 6 months. They were asked to keep a dysmenorrhea diary. The menstrual cramps were documented on a scale of 1-10, with 1 indicating slight pain and 10 indicating severe pain. The need for pain medication was documented by the test subjects. For the last 3 cycles, the patients were asked to use tampons with CBD oil. Five drops of 10% full-spectrum CBD oil were dripped onto a tampon by our patients themselves. During the use of CBD tampons blood was taken to determine the Cannabidiol content.

**Results:** The evaluation after the 3 months in which all patients used tampons soaked in 5 drops of 10% Cannabidiol oil yielded the following results: There was a significant reduction in menstrual pain. The pain scale readings fell by 2 to 3 points. The use of painkillers decreased.

**Conclusion:** Menstrual pain can significantly impact the quality of life for women. With the common practice of self-medication many individuals are often unaware of the potential side effects. Tampons infused with Cannabidiol oil could offer a promising alternative.

Clinical Studies

**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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**Background:** 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.

**Objective:** 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.

**Results:** Assessing the PK properties of the solid CBD formulation in healthy adults compared to an oily formulation using the AUC<sub>0-24h</sub> 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<sub>0-24h</sub> sums of all measured plasma levels of CBD, 7-OH-CBD and 7-COOH-CBD were covered in the objectives. All PK parameters: C<sub>max</sub>, T<sub>max</sub>, T<sub>1/2</sub>, AUC<sub>0-24h</sub> and AUC<sub>inf</sub> 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 regimens in open-label, 4-way crossover design.

**Conclusion:** The PK study design was defined according to good clinical practice standards.

## **Impurity Profiling and Discrimination between Natural and Synthetic Cannabidiol using a New HPLC Method with Multiple Detection Systems**

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**Background:** Cannabidiol (CBD) is a non-psychoactive phytocannabinoid extracted and purified from *Cannabis sativa* L. inflorescences. It can be obtained by organic synthesis also. It is an active pharmaceutical ingredient (API), given its usage in treating some types of paediatric epilepsy. For this reason, this compound requires a deep characterization in terms of purity and origin.

**Objectives:** This study is aimed to develop a new analytical method based on high-performance liquid chromatography (HPLC) with different detection systems to study the purity of CBD and define its origin on the basis of the impurity profile.

**Methods:** Qualitative and quantitative analyses of CBD samples were carried out by UHPLC-HRMS and HPLC-UV/Vis, respectively. In addition to  $\Delta^9$ -tetrahydrocannabinol ( $\Delta^9$ -THC) and  $\Delta^8$ -THC, other compounds, such as cannabigerovarin (CBGV), cannabigerol (CBG), cannabichromenvarin (CBCV) and cannabichromene (CBC), were examined as potential discriminating impurities. To definitely confirm the origin of CBD samples, the presence of other two minor impurities, namely cannabidihexol (CBDH) and cannabidiphorol (CBDP), was assessed as unequivocal for a natural origin. Principal Component Analysis was finally applied for statistical analysis.

**Results:** The chromatographic analyses confirmed the origin declared for seventeen natural samples and five synthetic samples, with the natural ones showing the characteristic presence of minor cannabinoids derived from the plant matrix (mainly CBDV and CBDB), which are totally absent in synthetic samples. Synthetic samples were characterized by very high CBD purity percentages (100%), while natural CBD exhibited purity ranging from 97.5% to 99.7%. Three synthetic CBD samples were found to be of natural origin, as further demonstrated by the analysis of the minor cannabinoids CBDH and CBDP.

**Conclusions:** The HPLC method developed represents a reliable tool for detecting CBD impurities, being capable of discriminating if it was obtained either by extraction from hemp inflorescences or by synthesis

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## Clinical Studies

**The Impact of Cannabinoid Therapy on Sleep Improvement in Patients with Chronic Pain: A Preliminary Study**

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**Background:**

Chronic pain is a prevalent and debilitating condition that significantly impairs patients' quality of life, including their ability to achieve restorative sleep. Sleep disturbances are highly common in individuals suffering from chronic pain, leading to a vicious cycle that exacerbates both pain and sleep issues. Recent interest has surged in the therapeutic use of cannabinoids, particularly THC and CBD, for managing chronic pain, but their specific impact on sleep quality remains underexplored.

**Objectives:**

This study aimed to evaluate the effectiveness of cannabinoid therapy in improving sleep quality among patients with chronic pain. The research sought to investigate both subjective experiences and objective measures of sleep, thereby providing a comprehensive understanding of the role cannabinoids may play in sleep regulation.

**Methods:**

A total of 67 patients with chronic pain and reported sleep disturbances participated in this 8-week study. Participants were randomly assigned to receive a standardized cannabinoid preparation containing THC and CBD or a placebo. Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI) and the Epworth Sleepiness Scale (ESS) before and after the treatment period. The degree of pain was also evaluated using the Numeric Rating Scale (NRS) to explore correlations between pain reduction and sleep improvement. The primary outcome measures included changes in PSQI and ESS scores, as well as the frequency of nocturnal awakenings.

**Results:**

The study revealed a statistically significant improvement in sleep quality in the cannabinoid-treated group compared to the placebo group. PSQI scores improved by an average of 35% in the treatment group, while the placebo group showed no significant change. ESS scores indicated a reduction in daytime sleepiness, suggesting that improved nighttime sleep quality led to better daytime functioning. Additionally, NRS scores showed a significant reduction in pain, which strongly correlated with improvements in both sleep quality and reduced daytime sleepiness.

**Conclusion:**

Cannabinoid therapy has demonstrated potential as a viable treatment option for improving sleep quality in patients with chronic pain. The findings suggest that cannabinoids may enhance sleep both by directly affecting sleep mechanisms and by alleviating pain, which in turn reduces daytime sleepiness. These results underscore the importance of further research into the long-term benefits and risks associated with cannabinoid use in this patient population, potentially paving the way for new therapeutic strategies in the management of chronic pain and its associated sleep disturbances.