Medical Cannabis and Cannabinoids

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Abstracts

Scientific Committee

Contents

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Disclosure Statement

The abstracts were reviewed and selected by the CannX Scientific Committee member, Dr. Yuval Zolotov. Dr. Zolotov has no conflicts of interest in connection with the selection of abstracts.

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Medical Cannabis and Cannabinoids

Abstracts

ORAL PRESENTATIONS

01. SCI: Innovations in Science and Medicine

O001

CANNABIDIOL DOWNREGULATES THE EXPRESSION OF THE HUMAN FAM111B GENE IN LUNG ADENOCARCINOMA

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Lung adenocarcinoma (LUAD) is the most common type of lung cancer, accounting for 38% of all lung cancer cases. It ranks among the top causes of cancer mortality due to emerging cancer drug resistance. The human FAM111B gene has recently been established as an essential gene for LUAD progression, making it a promising therapeutic target. This study sought to investigate the possible downregulation of the FAM111B gene by Cannabidiol (CBD) using quantitative real-time quantitative polymerase chain reaction (qRT-qPCR), Western blot and Immunocytochemistry in lung adenocarcinoma (A549) cell line. The results suggest that CBD downregulated transcripts and protein levels of the FAM111B. In addition, CBD similarly affects the downstream genes involved in cell-cycle regulation (p53, CCNB1, p21 and apoptosis (BAG3 and BCL2). Altogether, this study's data indicates that the reported anticancer properties of CBD, such as cell cycle arrest and apoptosis in A549 cells, might result from the downregulation of FAM111B.

O002

MEDICAL CANNABIS SIGNIFICANTLY DECREASES AVERAGE PAIN SCORE FOLLOWING ONLY THREE MONTHS OF USE

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Introduction: Pain is a common indication for medicating with cannabis in the USA. Patients may self-select the cannabis product and method of use, with guidance from qualifying practitioners and dispensary personnel. **Methods:** A retrospective review was conducted of a proprietary database of 600 patients with a primary pain condition certified to use cannabis between 08/2019 and 05/2020. Patients completed a pre-certification evaluation and a three-month survey to assess response to cannabis therapy. Five Numerical Rating Scale (NRS) assessments were used to quantitate pain response. Statistical evaluations included descriptive statistics, paired t-tests, and regression analysis. The study was exempted from IRB review. **Results:** Primary pain conditions included chronic (81.3%), back/neck (9.8%), arthritis (4.7%), neuropathy (1.8%), spinal cord injury (1.5%) and muscle spasm (0.8%). Most frequently used products included THC-dominant (44.6%), hybrid products (21.1%), and unknown strain (27.1%). Most patients reported using one method of consumption (48.7%), while 21.7% reported > three methods. The most common methods of use included inhalation (56.8%), edibles/tinctures (33.1%), and topical administration (5.9%). All but two patients (99.6%) reported at least one positive effect of cannabis, with pain reduction (86.1%) and improved sleep (63.9%) most improved. Statistically significant improvements in average pain scores were seen for all NRS measures. Patients reported an average of 16.5% (CI: 13.7–19.4, $p<0.001$) reduced pain. Average pain decreased by 0.69 (CI: 0.51–0.86, $p<0.001$), as well as interference with general activity (-1.03, CI: 0.79–1.27, $p<0.001$), interference with normal work (-0.98, CI: 0.72–1.23, $p<0.001$), and interference with enjoyment of life (-1.29, CI: 1.03–1.54, $p<0.001$). All but 6.2% of patients reported at least some level of improvement in pain relief or symptoms. 81.8% of patients reported a lessening of pain of at least two points. Novices had a higher increase in pain relief at three months compared to those with prior cannabis experience (-0.10, CI: -0.20 – -0.01, $p=0.032$). Prior cannabis experience, frequency of use, strain profile and method of consumption were not significant predictors of the improved NRS pain response, interference of pain with general activity, or enjoyment of life. **Conclusions:** These data support utilization of cannabis as an effective option for pain management.

O003

NOVEL CANNABIDIOL (CBD)-INFUSED ABSORBABLE IMPLANT DELIVERY SYSTEM FOR NEUROTRAUMA

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Traumatic brain (TBI) and spinal cord injuries result in profound local hypoperfusion, ischemia, chronic inflammation, and metabolic dysregulation which restrict drug delivery to the site of impact so that peripheral treatment alone would have limited access to the site of injury during the most critical phases of neurotrauma. Cannabidiol (CBD), the major non-psychotropic cannabinoid, has anti-convulsant, anti-inflammatory, anti-nociceptive, anti-oxidant, and immuno-suppressive properties

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which may abate neurotrauma-induced neuropathophysiology. We hypothesized that continuous local delivery of CBD directly to the contusion site overlying the dura of brain or spinal cord can attenuate the risk of excitotoxic Ca^{2+} hyperexcitability that causes progressive cell death leading to long-term behavioral and neuropathological sequelae, such as paralysis, locomotor impairment, memory and attention deficits, depression, as well as onset to intractable seizures. A patent pending CBD delivery system for brain and spinal cord in pre-clinical rodent models of contusion was devised. A controlled weight drop stereotactic apparatus was used to induce cortical or spinal cord injury. CBD was delivered over the contusion site (CBDi) in an infused gelfoam matrix and systemically by injection. Brains and spinal cords were paraffin sectioned, processed and analyzed with Nissl, NeuN and GFAP staining methods. In both neurotrauma models of injury, post-administration of the CBD-infused implant followed by subcutaneous administration reduced lesion volume and restored locomotor function. After TBI, CBD treatment also reduced defecation, decreased the loss of neurons in the ipsilateral hippocampus, reduced the number of acidophilic injured neurons of the contralateral hippocampus, and inhibited GFAP in the hippocampus bilaterally, which corresponded with improved learning and memory function in the alternating T-maze and increased time with novel objects compared to contusion alone consistent with restored cognitive function. The results suggest that dual therapy by targeting the site of injury internally with an infused CBD medical carrier that is supplemented systemically can offer a more effective countermeasure than systemic or implant treatment alone for opposing the deleterious effects of penetrating head and spinal cord wounds. Whether the beneficial effect of the dual CBD treatment was due to anti-inflammatory, anti-convulsant and anti-oxidative stress properties or other undefined mechanisms is yet to be elucidated.

O004

CANNABINOIDS AND CANNABIS EXTRACTS AFFECT METABOLIC SYNDROME PARAMETERS INCLUDING MICROBIOME IN MICE FED HIGH FAT-CHOLESTEROL DIET

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Introduction: Nonalcoholic fatty liver disease (NAFLD) is associated with metabolic syndrome, which often includes obesity, diabetes, and dyslipidemia. Several studies in mice and humans have implicated the involvement of the gut microbiome in NAFLD. While cannabis may potentially be beneficial for treating metabolic disorders such as NAFLD, the effects of cannabis on liver diseases and gut microbiota profile have yet to be addressed. In this study we evaluated the therapeutic effects of cannabis strains with different cannabinoid profiles as well as individual cannabinoids on NAFLD progression. **Methods:** NAFLD was induced by feeding mice a high fat cholesterol diet (HFCD) for 6 weeks. During this period cannabis extracts or individual cannabinoids were administrated orally at a concentration of 5 mg/kg every 3 days. Profile of lipids, liver enzymes, glucose tolerance and gene expression related to carbohydrate lipids metabolism and liver inflammation were analyzed. The effect of cannabis strains or cannabinoids on microbiota composition in the gut was evaluated. **Results:** A CBD-rich extract produced an increase in inflammatory related gene expression and a less diverse microbiota profile, associated with increased fasting glucose levels in HFCD fed mice. In contrast, mice receiving a THC-rich extract exhibited moderate weight gain, improved glucose response curves and a decrease in liver enzymes. Surprising HFCD fed mice given CBD alone exhibited improved glucose response curves, while THC alone did not affect glucose response. Similar effects on the microbiota composition were observed. **Conclusions:** The results of this study indicate that while administration of cannabis containing elevated levels of THC may help ameliorate symptoms of NAFLD, THC alone may not be as effective. Interestingly, while CBD alone may be beneficial at alleviating at least some of the symptoms of NAFLD, a CBD-rich cannabis extract may cause a pro-inflammatory effect in the liver, linked with an unfavorable change in the microbiota profile.

O005

METABOLIC EFFECTS OF MEDICAL CANNABIS TREATMENT

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Introduction: Cannabis has a wide range of favorable clinical effects on pain, sleep, mood, gastro-intestinal symptom, appetite and physical activity; factors that may affect the metabolic profile of the consumer. In this study, we prospectively evaluated patients recently starting medical cannabis treatment. **Methods:** All patients from the rheumatology clinic, who were just approved for medical cannabis treatment for resistant chronic pain, were recruited. After consent, demographic and clinical parameters were documented, including indication for medical cannabis treatment, way of consumption, type of cannabis and monthly dose of medical cannabis. Fasting morning blood glucose, hemoglobin A1c, insulin, lipid profile, cortisol and uric acid levels, in addition to body weight, were obtained just prior to and 3 months following cannabis consumption. Wilcoxon' sign rank test was used to compare baseline levels to those obtained 3 months later **Results:** Twenty-eight patients completed the study. Mean age of the patients was 47.8±9.1 years and ~70% were female patients. 75% of all the patients had fibromyalgia. Mean monthly consumed cannabis amount was 22.21±3.6 gr, and 21 (75%) patients used extracts (oil). There was no significant change in any parameter evaluated. **Conclusion:** The results of our study seem to indicate that medical cannabis, mainly extracts, have no significant effect on any parameter of the metabolic profile of patients with chronic pain syndrome, during 3 months of initial use.

O006

OBJECTIVE QUANTIFICATION OF THE IMPACT OF MEDICAL CANNABIS TREATMENT USING CANNABIS-RESPONSIVE BIOMARKERS

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Objective quantification of the impact of medical cannabis treatment using Cannabis-Responsive Biomarkers™ Medical cannabis (MC) shows promising results in treating complex medical conditions. The current "gold standards" to evaluate MC treatment rely on self-reported evaluation by the patient, or observation by the health care provider (HCP). These subjective methods are limited and often affected by the patient's pathophysiological and psychological state, as well as by the interaction with the HCP who assesses the treatment. Cannformatics is an early-stage cannabis-focused biotech startup developing a new class of metabolic biomarkers, Cannabis-Responsive™ (C-Res) biomarkers, from saliva as a tool to objectively quantify the impact of MC treatment with at least one active cannabinoid. In a recent FDA/IRB observational pilot study we demonstrated the ability of C-Res biomarkers to successfully quantify the impact of MC. Children diagnosed with autism and successfully treated with unique off-the-shelf physician-supervised MC were evaluated pre-MC treatment and at time of maximal impact. Samples from the ASD group (n=15) and a typically-developing control group (TD; n=9) were subjected to salivary metabolomics and lipidomics analysis. Ten minutes prior to saliva sampling, parents filled out behavioral rating surveys. Potential C-Res biomarkers exhibiting a shift towards the TD physiological levels were identified in children with ASD after MC treatment based on the physiological values determined in the TD group. A similar qualitative improvement trend in children with ASD treated with MC was also observed in the behavioral surveys. The potential C-Res biomarkers were categorized as anti-inflammatory, redox regulation, bioenergy-associated, neurotransmitters, amino acids, and endocannabinoids; and changes in their levels suggested MC treatment is involved in the regulation of the central nervous system and behavioral symptoms commonly observed in individuals with ASD. We will present additional C-Res biomarker applications, including (1) pre-dosing, which we will use in the future to recommend product and dosage based on one saliva sample pre-MC treatment; (2) time-dependent optimization of MC treatment; and (3) extension of the C-Res platform for other medical conditions treated with MC.

O007

PRE-CLINICAL TOXICITY OF CANNBIGEROL IN RATS AND C. ELEGANS

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Introduction: Cannabigerol (CBG) is becoming a more commercially available cannabinoid; however, very little is known about its acute or long-term toxicity and overall safety. Rodents and Caenorhabditis elegans (C. elegans), often used in models of safety and toxicity, were utilized in two studies to add to the scant pre-clinical safety literature on CBG. **Methods:** In C. elegans, acute and long-term toxicity was determined by exposing them to a wide range of CBG concentrations (0.075 μM, 0.75 μM, 7.5 μM, 75 μM, 375 μM, 750 μM, and 3750 μM) and assessing mortality, thermotolerance and motility compared to controls. Adult male and female Sprague Dawley rats were dosed orally with CBG (0, 35, 70, or 140mg/kg/day) for 14 days in a typical dose range finding toxicity study. **Results:** No acute or long-term toxicity was identified in C. elegans or rats treated with CBG. In C. elegans, CBG dose dependently increased resistance to heat-induced molecular stress (thermotolerance), extended mean lifespan (mortality) and increased the number of highly active animals late in life (motility) compared to controls. In rats there were no microscopic (liver, kidneys, adrenal glands), macroscopic, or clinical changes (body weight, food consumption) in any dose groups attributed to CBG. **Conclusion:** Acute and chronic exposure to CBG in C.Elegans and rats resulted in no observed toxicity (microscopic, macroscopic, clinical observations, mortality, thermotolerance, or motility) compared to controls. These studies begin to support the potential safety of CBG. Future work should examine a larger dose range, longer dosing period and pharmacokinetics (PK) in mammals and similar studies (PK) with the addition of pharmacodynamics in humans. Further, as many cannabinoid containing commercial products are complex, containing other cannabinoids, terpenes or other natural health products or ingredients, future work should also examine the impact these complex formulations may have on toxicity.

O008

CANNABIS USE IN GASTROINTESTINAL DISORDERS

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Genus Cannabis was classified into three species: C. sativa, C. ruderalis and C. indica. The Cannabis plant has been valued since ancient times. In India, Ayurvedic texts describe anti-inflammatory, antiseptic, and anti-convulsing properties of

Cannabis. The Chinese compendium of herbal medicine, (~2800 BC), recommended to be consumed as tea for gout, malaria, rheumatism, neuropatic pain, epilepsy and memory. Cannabis has been used for its medicinal purposes. Its consumption leads to the activation of cannabinoids receptors CB1 and CB2 that, through specific mechanisms can lead to modulation and progression of inflammation or repair.Genus Cannabis was classified into three species: C. sativa, C. ruderalis and C. indica. The Cannabis plant has been valued since ancient times. In India, Ayurvedic texts describe anti-inflammatory, antiseptic, and anti-convulsing properties of Cannabis. The Chinese compendium of herbal medicine, (~2800 BC), recommended to be consumed as tea for gout, malaria, rheumatism, neuropatic pain, epilepsy and memory. Cannabis has been used for its medicinal purposes. Its consumption leads to the activation of cannabinoids receptors CB1 and CB2 that, through specific mechanisms can lead to modulation and progression of inflammation or repair. The Cannabis plant contains 60 aromatic hydrocarbon compounds known as cannabinoids, including delta-9-tera-hydocannabinol (THC), which is primarily psychotropic. Another element, Cannabidiol (CBD), is efficacious in inflammation, motility and analgesia. In order to be pharmacologically usable, the active ingredients have to be consistent in concentration and potency. Innovative and precise medicine laboratory testing is required for the medical use of the plant extracts. The present work examines the efficacy of Cannabis in treating gastrointestinal disorders. Studies suggest that cannabis reduces issues associated with irritable bowel syndrome and inflammatory bowel disease. Manipulation of cannabinoid receptors also protects against liver injury; however, effects of cannabis extracts on the pancreas are controversial. Furthermore, cannabis helps to manage nausea, vomiting, anorexia, and weight loss, but benefits come with a risk of chronic cannabis misuse. As a result, more rigorous clinical trials must be performed to determine the safe prescription. In our laboratory we use a lymphocyte toxicity assay to personalize the effective use of cannabinoids in liver and gastrointestinal diseases.

O009

ADDRESSING THE OPIOID EPIDEMIC WITH RESEARCH AND REAL-WORLD DATA-INFORMED APPROACHES

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Background: The US opioid crisis continues to escalate and is exacerbated by the COVID-19 pandemic.[1] In 2019, synthetic opioids were involved in 70.6% of all drug overdose deaths (49,860 deaths).[2] From 2018-2019, no US State had a significant decrease in opioid overdose death rates.[2] The rollout of legal medical and personal cannabis use in the US may have a potential role in addressing the opioid epidemic.[3] Specifically, integrating medical cannabis therapies has been noted as a potential harm reduction method.[4] **Methods:** From 1/2017-10/2018 CannabisBPO partnered with the New Jersey Medical Cannabis program to survey patients regarding medical cannabis and poly-pharmacy. The Cannabis Center of Excellence (CCOE) from 2018-2021 surveyed cannabis consumers, patients, veterans, to understand their medical cannabis use patterns and associated clinical outcomes. CCOE studies are approved for ethical clearance by the UMass Dartmouth IRB. **Results:** The CannabisBPO study reported results from 3,948 New Jersey medical cannabis patients. The CCOE studies reported results from: Open Cannabis Consumers and Patients Study N=1,292 July 2018–Feb 2020; Veterans Health and Medical Cannabis Study N=565 March 2019–Jan 2020; COVID-19 and Cannabis Study N=481, May 2020–Aug 2021. In all studies, respondents reported reducing prescription medication use with cannabis, see Table 1. Additionally, CCOE study respondents reported cannabis use improves the quality of life and reduces other harmful behaviors, see Table 2. **Discussion:** According to 6,286 US cannabis patients and personal use consumers, many are actively using cannabis as an alternative to opiates and other medications, with the largest reduction observed in the most dangerous medication categories. Patients and healthcare providers need to be educated on the state of the clinical evidence and more research studies explored to develop public health and clinical interventions.

Table 1. Prescription Drugs and Medication Use Reduced using Cannabis (2017–2021)

Indicator	CannabisBPO New Jersey Study Jan 2017-Oct 2018 N= 3948(%)	CCOE Consumers and Patients study N=1,292 July 2018- Feb 2020 (%)	CCOE Veterans Health and Medical Cannabis N=565 March 2019- Jan 2020 (%)	CCOE COVID-19 and Cannabis Study May 2020 - Aug 2021 N= 481(%)
Not Actively Trying to Reduce Meds X% or [*Reduced Medications in the Past using Cannabis (X%)]*	N/A and *[(16%)]*	41% and *[(NA)]*	13% and *[(24%)]*	32% and *[(30%)]*
Reduction in Opiate Use	9%	19%	17%	14%
Reduced Anxiety Medications	15.5%	13%	14%	10%
Reduced Depression Medications	9.7%	22%	26%	19%
Reduced Inflammatory Medications	12.5%	N/A	17%	N/A
Reduced Blood Pressure Medications	3.3%	N/A	N/A	N/A
Reduced Sleeping Pills	14.5%	12%	4%	9%
Reduced Muscle Relaxers	13.4%	15%	16%	12%
Reduced Seizure Medications	1.8%	2%	11%	2%

Table 2. Impact on Quality of Patient Quality of Life in CCOE Studies 2018–2021

Indicator	CCOE Consumers and Patients N=1,292 July 2018-Feb 2020 (%)	CCOE COVID-19 and Cannabis Study May 2020 - Aug 2021 N= 481(%)
Generally helps with quality of life	77%	74%
Helps with psychological symptoms (e.g. anxiety, stress, calm, sadness, energy)	76%	84%
Helps with physical symptoms (e.g. body pains, function, sensation)	72%	65%
Helps to avoid starting other medicines (including opiates)	35%	30%
Helps to reduce use of alcohol	29%	42%
Helps to reduce use of opiates	19%	14%
Helps to reduce use of tobacco	12%	19%
Other (please specify)	6%	3%
Does not help my daily life	1%	1%

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O010

CANNABIS IN MIGRAINE

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Background: New York State (NYS) authorized cannabis for medically certified patients in 2015. No guidelines exist for the use of MC in chronic migraine patients. The limited body of literature for MC leaves providers underequipped and patients vulnerable. **Design/Methods:** This retrospective chart review of patients with CM, per International Classification of Headache Disorders (ICHD-3), examined 316 patients over the age of 21 with at least one month of MC through Dent Neurologic Institute. **Results:** On NYS MC, 83.2% (263) patients reported improvement in their headache profile. The average monthly migraine frequency change was a 42.1% decrease, from 12.7 to 7.4. Over half of the patients (171) reported improvement in their headache frequency, with 25.7% (44) experiencing ≥75% reduction of headache days. More than one third of patients, 38.3% (121), reported sleep improvement, 30.7% (97) reported anxiety improvement, and 24.7% (78) reported mood improvement. Twenty-eight patients used opioid pain medications for chronic migraine-related pain at the start of MC and 50% (14 patients) reduced their opioid consumption while on MC after an average of 5.6 years of opioid use. Less than a quarter, 23.1% (73), of patients reported side effects (SE), all mild or moderate severity. Patients taking a 20:1 (tetrahydrocannabinol: cannabidiol) ratio reported more headache profile improvement than patients on a 1:1 ratio (p=0.039). A high to low ratio carried a risk ratio (RR) of 1.97 for reduction in headache medications. A non-equal ratio carried a RR of 1.61 for mood improvement, with similar RR observed for anxiety (1.65) and sleep (1.70) improvements. There was no significant difference in SE among high to low, equal, or low to high ratios. Low to high ratios carried a negative RR for developing affective SE, such as fatigue and euphoria. **Conclusions:** MC may play a safe role in CM management by helping to improve headache profile, anxiety, sleep, mood, and opioid reduction. Future prospective studies are required to examine the role of MC in CM within a placebo-controlled environment. **Study Supported By:** Dent Family Foundation.

O011

POSSIBLE MODULATION OF THE NEURO-ENDOCRINE-CYTOKINE NETWORK BY THE PINEAL HORMONE MELATONIN AND CANNABIDIOL IN PSYCHOLOGY

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Today it is known that most human systemic diseases, including neoplastic, autoimmune and psychological pathologies, would be due to an alteration of the cytokine network, which plays a fundamental role in the regulation not only of the immune system, but of the overall main biological systems. At present, it is possible to modulate and regulate the cytokine network by the exogenous administration of those cytokines, whose endogenous secretion is abnormally diminished, or in contrast by the injection of monoclonal antibodies against those cytokines, whose endogenous production is excessively high. However, since cytokine secretion is physiologically under a neuroendocrine regulation, a new clinical approach to influence the cytokine network could consist of the exogenous administration of the major neurohormones or neuroactive agents involved in the neuroendocrine control of the immune functionless. At present, the pineal indole hormone melatonin and cannabidiol would represent some of the most promising agents, also because of their complete lack of toxicity and low cost. Until we will consider the clinical application of neuroactive immunomodulating molecules, such as MLT and CBD, as a simple pallative therapy of the untreatable human systemic diseases, no further advances in the Clinical Practices may be reached. On the contrary, by taking into consideration their effects on cell proliferation and immune functionless, it could be possible to control the clinical course of most human systemic diseases by acting on the central neuroendocrine regulation of the immune system through a modulation of the cytokine network, by abrogating the non-scientific difference between curative and palliative therapy of cancer, autoimmunity and psychiatry.

O012

FEMALES REPORT MORE ADVERSE EVENTS AND HIGHER NEGATIVE SUBJECTIVE EFFECTS IN MULTIPLE-DOSE TRIALS OF TWO ORAL MEDICAL CANNABIS PRODUCTS

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A growing number of females report using cannabis for medical purposes, and females vs. males report higher subjective response to acute doses of Δ9-tetrahydrocannabinol (THC). The purpose of this study was to examine sex differences after multiple doses of THC. Data were from two randomized, double-blind, placebo-controlled, multiple-dose trials of two oral medical cannabis products, respectively: Spectrum Yellow oil (20 mg cannabidiol (CBD), 0.9 mg THC / 1 mL of oil), and Spectrum Red softgels (0.3 mg CBD, 2.5 mg THC / softgel). Outcomes examined here did not differ between the two medical cannabis products; thus, data from the two trials were pooled for this analysis. Healthy adult participants (N=84) were confined to an inpatient research facility and randomized to receive 0, 5, 10, 15, or 20 mg total THC daily (dosed BID) for 7 days. Adverse events (AEs) were assessed throughout the trial, and the Drug Effects Questionnaire was administered pre-dose and 1, 2, 4, 6, 8, and 12 hours post-morning dose on Days 1, 3 and 7. Females experienced 3.2 (95% confidence interval=1.8–6.0) times as many AEs as males (87 vs. 13), especially for the System Organ Class of nervous system disorders (28 vs. 9). Relative to males, females reported significantly ($p<.05$) higher peak scores on negative subjective effects, including "anxious," "dislike the effects," "heart racing," and "paranoid"; females' higher ratings were constant across Days 1, 3, and 7. Females and males reported similar peak scores on positive subjective effects, such as "alert," "relaxed," and "euphoric/happy." In conclusion, females reported higher negative subjective effects to THC that persisted over a week of dosing. That females and males reported similar positive effects, however, suggests that the impact of sex on subjective effects varied by valence of effect. Future studies with large samples of medical cannabis patients are needed to probe females' nuanced response to THC. If replicated, results would have implications for sex-specific dosing strategies for medical cannabis products containing THC.

O013

EFFECT OF A CANNABIS EXTRACT ON ACUTE PAIN AND ON ANALGESICS REQUIREMENTS: A DOUBLE-BLINDED, RANDOMIZED, 24 HOURS FOLLOW-UP STUDY

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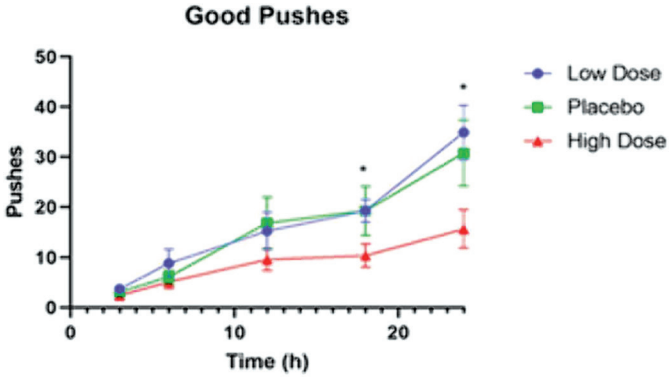
Background and aims: Medical cannabis consumers are a newer group of cannabis users, for whom the most frequent indication is managing chronic pain. There is only sparse data regarding the use of cannabinoids in acute pain conditions. Some have stated that cannabis has no role in management of acute pain while others have demonstrated primary evidence for opioid sparing and analgesic properties in post-operative or acute pain conditions. The aim of this pilot study was to examine cannabis analgesic function in acute radicular pain in humans. **Methods:** A double blinded, randomized, prospective study conducted on healthy adult patient's naïve to cannabis, admitted to emergency room with recent onset, acute radicular pain symptoms. Radicular pain symptoms had dermatomal pattern corresponding to physical exam and a recent CT/MRI, demonstrating intervertebral bulging lumbar disk. Patients were randomly divided into one of three groups: high dose (20 mg THC, 20 mg CBD), low dose (10 mg THC, 10 mg CBD) and placebo single sublingual administration. Patients were connected to a PCA (patient-controlled administration) morphine pump allowing self-administration of opioid for pain. Patients were followed up for 24 hrs with regard to pain, opioid consumption anxiety and other parameters. **Results:** 36 patients were recruited, 12 in each group. Patients receiving the higher dose of cannabis demonstrated a significant opioid sparing effect but no pain reduction. **Conclusions:** In this acute neuropathic clinical pain condition, we demonstrated significant opioid sparing effect in patient's naïve to cannabis who were administered one dose of sublingual high dose cannabis.



Low Dose vs. High Dose: 18h- p=0.03, 24h- p=0.02

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O014

THE CHEMOTYPES I AND III OF CANNABIS SATIVA L INDUCE DISTINCT TYPES OF CELL DEATH (APOPTOSIS / NECROSIS) IN HUMAN LEUKEMIC CELL LINES

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Cancer research in cells and animal models has evidenced the potential cytotoxic role of phytocannabinoids such us Δ-9-THC, CBD and CBG of leukemia, neuroblastoma, breast cancer, among others[1,2,3], through its interaction with different receptors of the Endocannabinoid System.[4] Studies conducted with clinically established chemotherapeutics, such as doxorubicin and epirubicin, have also shown that the induction of immunogenic apoptosis in cancer cells is directly associated with the success of antitumor therapy[5]. Based on these observations, this study aims to evaluate the cytotoxic activity in terms of the induction of death by early or late apoptosis of different Cannabis extracts on leukemic cells U937 y K562. **Methods:** Flowers from twelve (M1 to M12) different chemotypes of Cannabis (I, II, III) were collected. The cytotoxic activity of the Cannabis extracts (200 to 1.6 µg dry wt/mL) was evaluated in the human leukemic cell lines U937 and K562 for 48 and 72 h and assessed with the MTT methodology. The type of cell death (apoptosis/necrosis) was carried out with the extracts with an IC50 ≤ 36 µg/mL, using Annexin V-FITC and 7-Amino-Actinomycin D (7-AAD-PE) and immediately analyzed by flow cytometry (FACSAria I). **Results:** The extracts with the highest cytotoxic activity (IC50) for the U937 cell line were M3 (25 µg/mL), M5 (17 µg/mL), M7 (20 µg/mL) and M8 (30 µg/mL) and also induce early and late apoptosis in these cells. On the other hand, M8 (30 µg/mL), M9 (35 µg/mL), M11 (31 µg/mL) and M12 (36 µg/mL) were cytotoxic for the K562 cell line and also induced early and late apoptosis. **Conclusions:** Cannabis sativa extracts have different cytotoxic and pro apoptotic effects over the leukemic cells U937 and K562. The chemical analysis of the extracts showed that the plants with chemotype I (high THC) have pro apoptotic effects over the U937 cells. While the chemotype I and III (high CBD) induce pro apoptotic effects over the k562 cells. More studies are required to describe the Immunogenic cell death of Cannabis-derived compounds in human leukemic cells.

O015

ADHERENCE, SAFETY AND EFFECTIVENESS OF MEDICAL CANNABIS AND EPIDEMIOLOGICAL CHARACTERISTICS OF THE PATIENT POPULATION: A PROSPECTIVE STUDY

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Background: Despite the absence of rigorous prospective studies, there has been an increase in the use of cannabis-based medicinal products. During the study period, the use of medical cannabis in Israel was tightly regulated by national policy. We aimed to characterize the medical cannabis patient's population as well as to identify treatment adherence, safety, and effectiveness, through a prospective study of approximately 10,000 patients. **Methods and findings:** In this study of prescribed medical cannabis patients, adherence, safety, and effectiveness were assessed at six months. Treatment adherence was assessed by the proportion of patients purchasing the medication out of the total number of patients (excluding deceased cases and patients transferred to another cannabis clinic). Safety was assessed by the frequency of the side-effects, while effectiveness was defined as at least moderate improvement in the patient condition without treatment cessation or serious side-effects. We utilized logistic regression for the multivariable analysis of factors associated with treatment success. Most frequent primary indications requiring therapy were cancer (49.1%), followed by non-specific pain (29.3%). The average age was 54.6±20.9 years, 51.1% males; 30.2% of the patients reported prior experience with cannabis. During the study follow-up, 1,938 patients died (19.4%) and 1,735 stopped treatment (17.3%). Common side-effects, reported by 1,675 patients (34.2%), were: dizziness (8.2%), dry mouth (6.7%), increased appetite (4.7%), sleepiness (4.4%), and psychoactive effect (4.3%). Overall, 70.6% patients had treatment success at six months. Multivariable analysis revealed that the following factors were associated with treatment success: cigarette smoking, prior experience with cannabis, active driving, working, and a young age. The main limitation of this study was the lack of data on safety and effectiveness of the treatment for patients who refused to undergo medical assessment even at baseline or died within the first 6 months. **Conclusions:** We observed that supervised medical-cannabis treatment is associated with high adherence, improvement in quality of life, and a decrease in pain level with a low incidence of serious adverse events.

O016

DOUBLE-BLIND RANDOMIZED PLACEBO-CONTROLLED STUDY OF CANNABIDIOL CONTAINING FACIAL SERUMS

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Endocannabinoid system in the skin plays a role in many functions, such as healthy and balanced proliferation, differentiation, tolerance of skin cells, and the regulation of immune and inflammatory response. For this reason, there is more and more research into the topical use of cannabidiol (CBD), one of the cannabinoids in cannabis.

We performed a double blind, randomised, placebo-controlled trial of cosmetic facial serums that contain CBD. The study was approved by the Republic of Slovenia National Medical Ethics Committee. We recruited 20 healthy volunteers, who were using cosmetic products with CBD for 14 days and placebo products for 14 days, including wash-out period. The purpose of the trial was to assess how cosmetic products with CBD affect the skin in comparison with placebo, according to volunteer reports. Moisturising and oily face serums were tested. Volunteers got instruction to apply as much moisturizing serum, preferably in the morning and/or oily serum, preferably in the evening, as needed. After completed testing of all the products we used questionnaires to record and compare the subjective opinions of the volunteers.

On average, the volunteers estimated that the two CBD face serums outperformed placebo in the improvement of face skin elasticity, hydration and smoothness. The serums also improved skin dryness, decreased redness, and led to a small reduction of visible wrinkles and pores on the face.

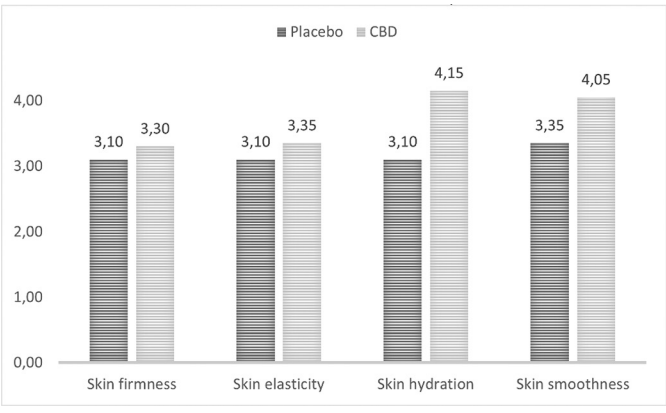

Fig. 1. Self-assessment after 14-day use of facial serum treatment. Scale: 1 - worsened, 2 - somewhat worsened, 3 - no change, 4 - somewhat improved, 5 - improved.

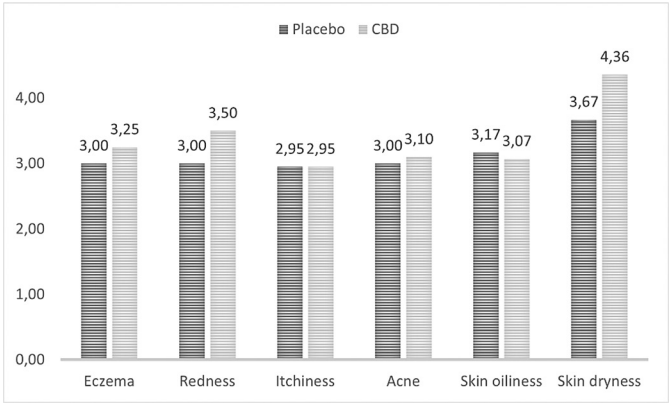

Fig. 2. Self-assessment after 14-day use of facial serum treatment. Scale: 1 - worsened, 2 - somewhat worsened, 3 - no change, 4 - somewhat improved, 5 - improved.

O017

VAPORISED MEDICAL GRADE CANNABINOIDS AS RESCUE MEDICATION IN ACUTE ANXIETY - A VALIDATION AUDIT OF ADULTS PATIENTS IN AN URGENT CARE DEPARTMENT

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Background: Acute panic attacks and anxiety is one the most prevalent psychiatric presentation in urgent/emergency care, with up to 1% of the yearly census. In the US, between 2009-11 there were over 1.2 million ED attendances related to this particular disorder, most discharged with benzodiazepines (BZD). The latter drug is known for its addictive potential and linked to a series of adverse outcomes. **Objectives:** During the derivation phase, to mitigate acute symptoms we offered vaporised THC-rich medical grade cannabinoids (vMGC) to patient presenting with acute panic attacks AND were not naive to smoke/vape cannabis when stressed. To validate our derivation concept we conducted a retrospective audit. **Design:** A case series of three consecutive adults with acute panic attack was identified during hypothesis generation. During validation we collated anxiety scores taken quarterly from every patient presenting with anxiety mood disorders (AMD) and treated with vMGC. **Results:** During derivation, in patients presenting at our Urgent Care Department with anxiety/panic attacks we observed cannabis use with higher prevalence than in the unselected adult population. As both in the derivation and the validation phase we only had a small dataset (n_1=3; n_2=42), significance tests were deterred and results were reported descriptively. **Limitation:** Single centre observation with low participant number in a jurisdiction where recreational cannabis use is prosecuted but medical use is legal. **Discussion:** Patients presenting in urgent/emergent care with panic attacks often disclose use of cannabinoids as a rescue measure however, it is unsure if it is a cause or causation. Evidence-based research in the field of MGC in general is often driven by self-reported user data, in AMD in particular the results are inconclusive. However pharmacological rationale and

empirical data suggest that MGC might be an alternative of BZDs and/or or may help reducing preexisting BZD use in acute panic attacks. Such observations warrant further longitudinal research centred around harm reduction in adults with AMD. **Conclusion:** Further multicentre, prospective validation is needed to investigate the potential role of MGC/vMCG in AMD. If patient safety is proven, medical cannabinoids might help improving patient satisfaction and reducing attendance rate in the ever-crowded urgent care departments.

O018

HARNESSING CANNABIS MOLECULES TO FIGHT INFLAMMATION-ASSOCIATED DEPRESSION

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The results of clinical surveys, cross-sectional and longitudinal studies on the relations between cannabis use and depression in humans are inconclusive, and to date no proper RCTs have been conducted to evaluate the antidepressant effects of cannabis or its components. In contrast, studies in experimental animals demonstrated that some cannabinoids, particularly CBD, as well as a few other cannabis molecules, have antidepressant potential in various models of depression. The current study aimed to further elucidate the antidepressant effects of CBD, the mechanism underlying these effects and the possibility to potentiate these effects by administering CBD together with additional cannabis molecules or adjunctive therapeutics in mice. Given previous findings from our laboratory, showing that peripheral and central inflammatory processes, and particularly microglia activation, can underlie the development of some forms of depression, we focused on the mediation of the behavioral effects of CBD-based therapeutics by modulation of microglia activation. We report that in cultures of BV-2 microglia cells, stimulated in vitro by various immune challenges (including LPS, Poly I:C or a-synuclein), CBD induced marked suppressive effects on the secretion of proinflammatory cytokines (TNFa, IL-6 and IL-1b). Combinations of CBD with specific terpenes or flavonoids indued synergistic microglia-suppressive effects. In vivo, CBD treatment in mice attenuated the development of depressive-like symptoms induced by administration of the inflammatory/microglial stimulator LPS. This effect was particularly demonstrated in mature (8 months old) as compared with young (2.5 months old) male mice, with no effects in either young or older female mice. In contrast, a microglia-suppressive combination of CBD with a specific flavonoid produced significant antidepressant effects also in female mice. Combinations of CBD with the NSAID (COX-2 inhibitor) celecoxib also produced synergistic suppressive effects in BV-2 microglia cultures in vitro, as well as potentiated antidepressant effects in the LPS model and the chronic social defeat stress model of depression in mice. Together, these studies suggest that microglia-suppressive cannabis-based formulations may serve as efficacious antidepressants. Such treatments should be administered in a personalized medical approach, targeting depressed patients with an elevated inflammatory status (determined by blood testing of inflammatory markers).

ORAL PRESENTATIONS

02. BIZ: New Technologies, New Opportunities

O019

EVIDENCE-BASED CUSTOMER DISCOVERY AS A FIRST STEP FOR DEVELOPING A DECENTRALIZED CLINICAL RESEARCH PLATFORM FOR MEDICAL CANNABIS

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Objectives: The National Science Foundation's Innovation Corps (I-Corps™) program was developed to train scientists & engineers in innovation skills, providing a framework to transform their ideas into commercial successes. One of these skills, evidence-based customer discovery (EBCD) is a qualitative research methodology that helps innovators focus on understanding the problems their potential customers face and to determine if they would want to use a product or service, before actually developing it. The nascent medical cannabis industry is highly-regulated and quasi-legal, leading to research hurdles and severe under-funding. The goal of this project was to use the EBCD method to assess customer segments, along with their obstacles and interests when considering development of a decentralized on-demand research platform to support clinical research for medical cannabis. **Methods:** As part of our participation in the Rutgers University I-Corps™ program, we developed customer segment descriptions and corresponding value proposition hypotheses for our research platform. We conducted semi-structured interviews with a diverse group of stakeholders to test our hypotheses and generate insights. Interviews took place over the course of approximately three months. Interviews were conducted online, recorded, and transcribed prior to validating the value proposition hypotheses, which were tracked using the software Innovation Within. We had a predetermined requirement for >80% aligned insights for 'validation'. **Results:** In total we conducted 47 interviews with 15 researchers (academic/hospital settings), 14 employees of medical cannabis producers, 9 health-care providers (HCPs) who actively recommend or prescribe medical cannabis, 6 regulators/policymakers for medical cannabis, and 2 healthcare consumers. Interviewees resided in North America (72%), EU/UK (15%), and Israel (13%). Value propositions hypotheses were confirmed as 'valid' for researchers, producers, and HCPs, with >80% alignment of insights. Additional customer needs and potential platform features were highlighted. **Conclusions:** EBCD is a crucial first step in determining potential

success of a product or service before it reaches the market. We used direct dialog with key customers to 'validate' our hypotheses around the need for a decentralized on-demand clinical research platform specific for medical cannabis. This process allowed us to gain evidence for product-market fit, and to learn about particular features of interest.

O020

WHY PORTUGAL MAY BE THE IDEAL HUB FOR MEDICAL CANNABIS IN EUROPE?

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Why Portugal may be the ideal hub for medical cannabis in Europe? Portugal is setting itself to become the medical cannabis production powerhouse serving growing European markets. The largest European shipment of medical cannabis within Europe have been taken place from Portugal to Germany. But why is Portugal such an attractive country for the medical cannabis business? There are some factors that make Portugal an excellent hub for the development of medical cannabis market, but what attracts investors' attention is mainly the climate, which allows for a minimum use of energy to maintain the conditions necessary for the plant growth, making production costs more affordable. Labor costs are also cheaper for employers, when compared to other European countries, and the high competence of Portuguese professionals has been differentiated, mainly in the areas of engineering, pharmaceuticals, and biomedical sciences. Another aspect is the political stability that led to the approval of the legalization of medical cannabis in the Parliament with a majority in favor. Portugal benefits from a very clear and favorable regulation. Thus, the industry is regulated by Infarmed, Portuguese authority of medicines and health products, which has a great reputation at European level, in other words a license granted by this entity has very high value at the European level and for other markets as well". The emerging growth in Portugal is remarkable and expectations on what is called "green gold" are expected to continue to grow in line with the trend.

O021

A NOVEL EDUCATIONAL TOOL FOR DISPENSARY STAFF AND PATIENTS: MEDICAL CANNABIS EDUCATION APP

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Medical cannabis utilization in the United States continues to grow exponentially with legal reform allowing expanded individualized access for patients. Cannabis dispensaries face a challenge of providing adequate education to these patients. Limited survey data suggested that medical cannabis patients may lack a foundational knowledge of cannabinoid therapy. For this reason, our team created an electronic application designed for dispensary staff and patients. The objective was to address a perceivable knowledge gap and to achieve a core competency of baseline medical cannabis education. Through survey and discussion, we perceived that this target audience of adult patients would be motivated to hone educational content and enrich knowledge when they have ready access to the app on their phones. This app, named MedCannEdAPP, was created via collaboration with a private entity, Euphoria Wellness (New Market, MD). The five course modules include cloud-based materials, ADA (American Disabilities Act) compliant PowerPoint slides with transcripts, infographics, videos, peer-reviewed articles, and blogs through the app. The instruments for the evaluation plan are based on Level 1 (Reaction) and Level 2 (Learning) of Kirkpatrick's levels of evaluation. This application enabled deeper understanding of the educational requirements of stakeholders to inform future enhancement of the educational tool. We also determined best practices of using assessment and feedback to gauge the success of this program. We feel this educational platform may form a fundamental basis for education of important stakeholders in the medical cannabis space and conveniently fills an unmet need for patients and dispensary staff.

O022

CONTROLLED AND RAPID DRYING OF MEDICAL CANNABIS INFLORESCENCES BY RADIO FREQUENCY METHOD

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One of the main steps in the manufacturing process of medicinal Cannabis is drying. Most current drying methods in the Cannabis industry are relatively slow and inefficient processes. This work presents a drying method based on solid-state radio-frequency, and examined its efficiency for drying Cannabis inflorescences compared to the traditional drying method. This method resulted in a considerable reduction of drying time, from several days to a few hours. The volumetric heating induced by the radio-frequency penetrates into the inner part of the Cannabis inflorescences and resulted in a more uniform drying between the surface and the inside. The multiple frequency-phase combination states of the system allowed a high degree of control and prediction of moisture levels during drying, thus preventing over-drying. A range of drying temperatures was tested (40°C, 50°C, 60°C and 80°C) and a drying temperature of 50°C provided the most effective results in terms of both short drying time and preservation of the secondary metabolites composition compared to traditional drying. At 50°C, the chemical profile of phytocannabinoids and

terpenoids was best kept to that of the original plant before drying, suggesting less degradation by chemical reactions such as decarboxylation. The fast-drying time also reduced the susceptibility of the plant to microbial contamination. Thus, radio-frequency drying is an effective post-harvest step to quickly dry the plant material for improved downstream processing with a minimal negative impact on product quality.

ORAL PRESENTATIONS

03. AGR: Advanced Agriculture and Production

O023

PRODUCTIVITY EFFECTS OF THREE SINGLE PLANT GROWTH PROMOTING RHIZOBACTERIA INOCULATION ON CANNABIS SATIVA L. GROWTH AND FLOWER YIELD AND CANNABINOIDS PROFILE

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Cannabis production is demanded which response to its various end-use applications including medical and recreational purposes. An important challenge is achievement of high yield with minimum input for indoor production. The beneficial phytomicrobiome as a sustainable approach gives its potential and ability to enhance plant growth has already been evaluated for a range of plants. A series of studies were conducted to evaluate three individual plant growth promoting rhizobacterium (PGPR, Bacillus sp., Mucilaginibacter sp. and Pseudomonas sp.) on cannabis (cv. CBD Kush) cuttings' root development and subsequent plant growth. When compared to control (mock inoculation with $MgSO_4$), inoculation with PGPR increased root length at vegetative stage by 12.96 and 17.48%, and 32.08%, in response to strain A, B and C inoculation, respectively. In addition, inoculation of PGPR enhanced flower fresh weight by 5.13%, 6.94% and 11.45%, inoculating with Bacillus sp., Mucilaginibacter sp. and Pseudomonas sp. respectively. While the plant height, node number, branch number and leaf area treated with PGPR was rarely different from control. Throughout growth (vegetative and reproductive), inoculation with Pseudomonas sp. resulted in the greatest increase in photosynthetic rate mainly in the flower formation stage, harvest index, while Bacillus sp., Mucilaginibacter sp. resulted in greater flower number and axillary bud outgrowth rate. This study provided a plasticity result of cannabis in terms of response to the specific beneficial microbes, which was expressed through effects on morphology, physiology (over time), and biomass yield.

O024

VEGETATIVE PROPAGATION EXPERIMENTS ON MEDICINAL CANNABIS (CANNABIS SATIVA L.)

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The rooting trial of the crop medicinal cannabis (Cannabis sativa L.) has been conducted in enclosed climate-controlled plastic tents within a glasshouse compartment at Wageningen University & Research. Stem cuttings were taken from White Widow (WW) and Afghani (A) motherplants from stem cuttings, and from tissue culture, both grown for 3 months. Stem cuttings were stored up to 61 days and propagated in stonewool cubes. Adventitious rooting was qualitatively scored and fresh weight was determined. Cultivar Afghani showed superior rooting when compared to White Widow. No difference was seen in adventitious rooting between stem cuttings taken from motherplants that were grown from stem cuttings and from tissue culture. Cold storage duration did not affect the ability to form adventitious roots. At this moment we are conducting more research on vegetative propagation of medicinal cannabis. These include the effect of stem cutting type (mid cutting, and top shoot cutting with one or two fully expanded leaves), plant density in propagation (208, 312 and 624 plants m^{-2}), rooting supplements (Clonex 0.3% IBA gel, Rhizopon 0.3% IBA powder, hydrogen peroxide (H_2O_2) (3.5% w/v) solution, and Aloe Vera powder), substrate volume, and light intensity on adventitious rooting. Further research will be conducted in 2022 to determine the effect of the greenhouse climate on sugar and auxin levels within the motherplants, and subsequently on adventitious rooting of stem cuttings. Upon selection for CANNEX we would like to discuss with the organizers which (or maybe all) results would be of interest to present to the scientific community.

O025

UTILIZATION OF BENEFICIAL AND HIGHLY-EFFICACIOUS PHYTOMICROBIOME TECHNOLOGIES EFFECTS IN PRODUCTION OF CANNABIS SATIVA

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Cannabis is an extraordinarily interesting plant in terms of research. It has multiple uses: fiber, food and medicinal (both sedative and psychoactive) materials. Humans have utilized cannabis in these various capacities for many 1000s of years, and there are cultures where cannabis use is long-term embedded. However, much of what we now understand about plants has been learned over the last 100 years and throughout almost all of that time work on cannabis has been prohibited, so there is a substantial amount of catching up to do, particularly in the areas related to specific utilization of cannabis, such as matters related to cannabinoids.

We now understand that a plant is accompanied with a substantial, complex and carefully orchestrated population of microbes, the phytomicrobiome, most of which are beneficial through performing specific activities for the plant. It is now generally recognized that evolution acts on the combined entity resulting from the plant and its associated microbes, now known as the holobiont. We have conducted research on regulation of elements of the phytomicrobiome and their regulation of the plant, through signal compounds, effective at very low concentrations (as low as 10^{-11} M) – essentially hormones of the holobiont. We have isolated, identified and commercialized some of these. There has been very little research on effects of the phytomicrobiome on cannabis plants and their products. Because there is concern around the application of chemical inputs for control of pest organisms or promotion of plant growth during Cannabis production bio-derived alternatives, often effective at extremely low concentrations, would be a valuable development for this crop. Thus, plant beneficial microbes from the phytomicrobiome, or materials such as signal compounds produced by them, should be explored and developed as potentially safe, low input and sustainable inputs for cannabis production.

POSTER PRESENTATIONS

01. SCI: Innovations in Science and Medicine

P001

NITROGEN CONTAINING CANNABINOLIC ACIDS DERIVATIVES AS A NEW ANTICANCER DRUGS

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Intensive research of the main products of the cannabis plant - tetrahydrocannabinolic (THCA) and cannibidiolic (CBDA) in recent years provided supportive evidence for their anti-inflammatory and anticancer activity, as well as the absence of any psychoactive properties. The presence of a carboxyl group in the cannabinoid acid molecules opens up a truly "Klondike" opportunity to obtain different derivatives and study their biological activity. The synthesis of THCA and CBDA nitrogen derivatives and followed in vitro anticancer screening on various cancer cells such as T47D (breast), U251, U87MG (brain), A549 (lung), PC-3 (prostate), TE-6 (esophagus), Caco-2, HT-29 (colon), OPM-2, U266 (myeloma), SK-HEP-1 (liver), PANC-1, AsPC-1(pancreas) allowed to identify several compounds with activity at the 1.3-10 mM level[1]. Two THCA derivatives, ALAM027 and ALAM108, have been shown to suppress tumor growth in vivo to a level that is comparable to that of established anticancer drugs such as gemcitabine and paclitaxel in the human PANC-1 pancreatic tumor xenograft model[2]. It should be noted that these compounds were administered orally as oil-based solutions, as opposed to via injection as is the case for many of the established cancer drugs. Thus, the use of cannabinoid acids as starting compounds for the synthesis of novel derivatives can be considered as the next significant stage in the evolution of cannabinoid anticancer research.

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P002

CANNABIS PRODUCTS IN POORLY REGULATED MARKETS: PUBLIC HEALTH, ETHICS, AND MESSAGING

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Background: In the United States, cannabis products are marketed and sold in the context of a highly diverse and disjointed set of regulatory systems across approximately 38 States. Cannabis consumers can now choose from a diverse array of cannabis products sold in medical cannabis dispensaries and commercial stores. These products range from plant material, solid and viscous concentrates, preloaded cartridges, edible products (e.g., drinks, baked goods, candies), pills, tinctures, creams, and patches. The types and ratios of cannabinoid compounds (THC, CBD, CBG, etc.) in these products range widely as does the information on product labels. State laws and cannabis marketing materials directly and indirectly imply that these products confer numerous physical and mental health benefits to the consumer but offer little to no evidence-based guidance on which product to use and how much to administer. The absence of clinical efficacy data to guide dosing of any of these products for most health indications combined with the well-known potential for adverse effects related to delta-8 and delta-9 THC raises important questions about self-regulation of the cannabis industry and its intersection with governmental policy and regulatory efforts. **Method:** This poster will provide findings from multiple, national web-based survey studies of approximately n=15,000 regular cannabis consumers to illustrate how product regulations may impact cannabis consumption patterns – frequency, quantity, potency, and specific routes of administration of cannabis products. **Findings:** Suggested regulatory targets for product development, marketing, sales, and labeling are provided based on these findings and prior work on adverse effects of THC-laden cannabis products. **Conclusions:** Enhanced government regulation or self-regulation by the cannabis industry is necessary to mitigate the potential harm from use or misuse of many available cannabis products.

P003

THERAPEUTIC DRUG MONITORING OF CANNABIDIOL AND IMMUNOSUPPRESSANTS IN A KIDNEY TRANSPLANT PATIENT. CASE REPORT

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Introduction: Chronic pain is a very frequent complication in kidney transplantation. CBD is extensively metabolized by hepatic hydroxylation and oxidation involving CYP3A4 and CYP2C19 isoenzymes but can also undergo direct conjugation by Phase II enzymes. Cyclosporine (CYA) is extensively metabolized in liver and in intestine by CYP3A4, whith potential pharmacokinetic interactions with drugs that use the same pathway or that can induce or inhibit this enzyme. Mycophenolate is absorbed and transformed into mycophenolic acid (MPA), its active metabolite, by carboxylesterases located in the enterocyte and liver. **Objective:** Assess benefit and safety of CBD in chronic neuropathic pain, and its possible interactions with CYA and MPA in this patient Methodology: Close therapeutic monitoring with creatinine, liver function, hemogram and plasma determinations of MPA, CyA and CBD. **Results:** Fifty-year old male received his first renal transplant in 2018 starting with tacrolimus, with severe neuropathic pain as main complication. NMR and conduction studies were not conclusive. Pregabalin was started unsuccessfully. Tacrolimus and pregabalin were changed to cyclosporine (Cya) and gabapentin, respectively. Immunosuppressive treatment consisted of Cya 50 mg/8 am and 75 mg/8 pm, mychophenolate mofetil 1 g/12 hours and 5 mg prednisone a day. CBD was started with rising doses. Cya concentrations decreased requiring dose adjustment to 100 mg every 12 hours. MPA concentrations decreased as well. After a month under CBD treatment(1,6 mg/kg/day) no improvement in pain management was observed and CBD was discontinued. **Conclusions:** An important decrease in CYA levels was evidenced on day 9 and day 16 after starting the treatment with CBD, which required an adjustment of CYA. This suggests a possible induction of CBD on CYP3A4, the main metabolizing enzyme of CYA. Mycophenolate is activated to MPA by carboxyl esterase enzymes (CES); CES1 in intestine and CES1 and CES2 in liver. The inhibition of CES1 by CBD could explain the progressive decrease of MPA. Lower CBD plasma concentrations were evidenced on days 23 and 30, coinciding with the increase in the doses of CYA. This could be due to the high variability in the bioavailability of CBD after sublingual administration. Consequently, therapeutic drug monitoring is recommended.

	Day 1	Day 9	Day 16	Day 23	Day 30
Creatinine (mg/dl)	1,51	1,34	1,51	1,68	1,65
Hb (g/dl)	13,4	12,5	12,1	12,3	11,8
Hto (%)	40,6	37,3	36,5	36,5	35,4
Leukocytes (mm3)	6560	6370	5890	7050	6320
Platelets (mm3)	172000	138000	158000	189000	175000
Bilirrubin (mg/dl)	0,74	0,34	0,45	0,69	0,57
AF (U/l)	69	71	68	69	67
ALT (U/l)	17	37	16	13	15
AST (U/l)	17	21	17	15	13
C2 CBD (ng/ml)	SD	118	128	39	58
C2 CyA (ng/ml)	603	218	222	720	710
C0 MPA (mg/l)	10,6	7,8	4,4	4,2	4,5
Dose CBD (mg)	15,8/31,6	47,4/47,4	63,2/63,2	63,2/63,2	63,2/63,2
Dose CyA (mg)	50/75	50/75	50/75	100/100	100/100
Dose CBD (mg/kg/d)	0,6	1,2	1,6	1,6	1,6

P004

MEDICAL CANNABIS AND QUALITY OF LIFE IN PEOPLE LIVING WITH HIV

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If we look at health from a quality of life perspective, and while we know that cannabis is not the first choice for the treatment of many diseases, we realize that it will play an invaluable role in improving the quality of life for people suffering from chronic diseases, including those living with HIV. Given the benefits of cannabis use that we have observed in a number of common symptoms and complications of HIV infection, including loss of appetite, depression, neuropathy and difficulty sleeping, among others, we wanted to understand the benefits of using, over four years, cannabis oil above 15% CBD content, in 100 patients being followed-up in our institution. Data were collected during consultations and through a questionnaire. Clients, mostly men (72%) continue to report significant improvements in several symptoms: appetite (98%), nausea (93%), depression (90%), anxiety (93%) and sleep (96%), muscle pain (96%), nerve pain (83%) and paresthesia (91%). Most users (85%) assume improvements in their emotional and social performance which also had repercussions on their physical performance leading to an improved perception of health and general well-being. Everyday activities such as self-care with food and physical activity, leisure and relaxation moments were impacted by the improvement of lower anxiety and depression states, which had repercussions on quality of life, considering the circumstances experienced by the pandemic due to COVID-19.

P005

HUMAN MILK FEEDING AND CANNABIS USE: RECOMMENDATIONS FROM THE FIELD POST CANNABIS LEGALIZATION IN VERMONT

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Aim: Human milk feeding (HMF) is associated with many health benefits for the parent and child but there is very limited scientific research regarding the effects of cannabis use during HMF. Recreational cannabis became legal in Vermont in 2018. The purpose of this study was to replicate Bergeria and Heil (2015) by surveying lactation professionals on their recommendations regarding HMF and cannabis use one year after the legalization. **Methods:** A sample of lactation professionals attending the 2019 Vermont Lactation Consultant Association conference completed a survey regarding their recommendations on HMF and cannabis use. **Results:** Responses represented a significant change from the 2014 survey results in that fewer respondents in the most recent survey endorsed stopping HMF (15.2% vs 3.6%; p=.03) and a greater percentage endorsed a factor-dependent stance (44.1% vs 64.3%; p=.03). **Conclusion:** The current study examining recommendations regarding HMF parents who cannot stop using cannabis found that there was an increase in the percentage of lactation professionals who reported their recommendation was factor dependent and a decrease in the percentage of respondents who recommended parents discontinue HMF when compared to recommendations made in 2014 (Bergeria & Heil, 2015), before the legalization of recreational cannabis in Vermont. There was also an increase in respondents who reported their stance was based on the AAP policy statement, the ABM guidelines, and their state's child protective services policies when compared to responses in 2014. The shift toward less definitive answers on stance could be an indication that lactation professionals are having more nuanced discussions regarding cannabis use and HMF. It is possible that the legalization of recreational cannabis in Vermont played a role in stimulating these discussions and required lactation professionals to address these issues in their practice directly. The changed legal status of cannabis in Vermont could also explain the increase in the percentage of respondents who reported that their recommendations were based on AAP and ABM guidelines. Cannabis legalization might have required professionals to deliberately research and become familiar with the relevant latest guidelines from their professional organizations and to formalize policies in their workplace.

P006

INHIBITION OF HEPATOCELLULAR CARCINOMA GROWTH AND LIVER FIBROSIS BY NANOMOLAR CANABINOID CONCENTRATIONS

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Background and Aim: Cannabinoids bind to the CB1 and CB2 receptors regulating the function of multiple organs and tissues of the body. Interestingly, cannabinoids also bind to the Gi protein associated A3 adenosine receptor (A3AR), up-regulated in inflammatory and tumor cells. Can-Fite research shows that A3AR agonists can knock down inflammation and cancer via the specific induction of apoptosis in these cells. The goal of the current study was to investigate the anti-growth effect of cannabinoids towards hepatocellular carcinoma and fibrotic in the liver and the molecular mechanism involved. **Methods:** Hep-3b hepatocellular carcinoma cells and LX-2 stellate cells were cultured for 48 hours in the presence and absence of 10 nM CBD-rich THC3/CBD15 (T3/C15) and the A3AR antagonist MRS1523. ^{3}[H]-thymidine proliferation assay, and Western blot analyses were performed. **Results:** CBD-rich T3/C15 significantly inhibited Hep-3b and LX-2 cell proliferation (56%± 5.5 ; $p < 0.05$ and 37.4%± 4.0 ; $p < 0.05$, respectively). This response was neutralized by the A3AR antagonist MRS1523. Growth regulatory proteins down-stream to A3AR activation, including p-Akt, NF- kappa B, GSK-3β and β-catenin were all down-regulated. **Conclusion:** Our findings highlight the ability of CBD-rich T3/C15 in nanomolar concentrations to inhibit the growth of hepatocellular carcinoma and liver stellate cells via A3AR activation and de-regulation of the Wnt/β-catenin pathway. The findings open a novel therapeutic opportunity in liver cancer and fibrosis with minute CBD concentrations and low content of psychotropic THC fraction.

P007

CANNABIS STRAINS AND CANNABINOIDS PLAY KEY ROLE IN MODULATION OF NEUROINFLAMMATION

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Multiple sclerosis (MS) is a widespread chronic neuroinflammatory and neurodegenerative disease. Microglia play key role in the pathogenesis of an animal model of MS (experimental autoimmune encephalomyelitis) (EAE) via releasing cytokines and reactive oxygen species as nitric oxide (NO). The effect of cannabigerol (CBG) itself on microglial inflammation (low and high inflammation grades) and EAE induced splenocyte inflammatory response has been hardly investigated before. In this study, we aimed to investigate the effect of CBG on microglial inflammation (different

grades), neurological scoring and inflammatory cells' response in EAE mice. In the present study, CBG attenuated microglial production of NO, inducible nitric oxide synthase (iNOS) and tumor necrosis factor- α (TNF-α) stimulated by the inflammatory inducer, lipopolysaccaride (LPS) at different concentrations. CBG significantly reduced the MOG-induced astrocytosis in lumbar sections of spinal cords. It also significantly decreased neuronal loss shown to be induced by MOG peptide in these sections. All MOG-treated mice developed a severe disease that peaked by day 15 post immunization. In contrast, the clinical manifestations of EAE were attenuated in mice receiving four injections of CBG at days 12 to 15 upon immunization. In a therapeutic prospective, our results suggest that CBG may represent a therapeutic opportunity in MS, based on its multi-target properties.

P008

INHALED CBD PHARMACOKINETIC PROFILE IN RATS

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Introduction: Inhaled cannabidiol (CBD) use has been steadily increasing, though safety and pharmacokinetic (PK) effects have been minimally studied. To examine PK of inhaled CBD, rats were exposed to an aerosolized CBD/propylene glycol (PG) mixture, blood was drawn and plasma analyzed. **Methods:** Adult male Sprague Dawley rats were exposed (nose only) to aerosol comprised of 41% CBD and 59% PG or Air control, doses were established by increasing the duration of exposure. Blood was drawn at various time points to characterize PK of inhaled CBD. A separate group of male rats were dosed orally with a single CBD dose (in medium chain triglyceride (MCT) oil) and had blood drawn at the same time points for a rough comparison of inhaled and oral CBD PK profiles. Blood was spun down and plasma was analyzed for CBD and its major metabolites. **Results:** Dose-dependent PK effects were observed for inhalation of CBD. CBD and metabolites were quantified in plasma after dosing via inhalation or oral gavage in male rats. CBD delivered via inhalation reached peak plasma (~731ng/mL) ~5 minutes following exposure compared to a peak at ~2 hours (~107ng/mL) for the rats dosed with CBD orally. **Conclusion:** Inhaled or orally delivered CBD, resulted in a dose-dependent (inhaled) PK response with a typical PK profile for each route of administration; rapid, high peak for inhaled, slower, and lower peak for the oral route of administration. Future work conducted in humans will help to determine PK under normal use conditions. This study was limited in that the aerosol used for exposure was generated by nebulizer and not a commercially available e-vape device. Another limitation of comparing inhaled to oral routes of administration in rodents is the dosing period; while an oral injection is a fast bolus dose, inhalation takes minutes of continuous exposure to reach the achieved dose, meaning that metabolism is occurring as dosing continues. The current study adds to scant literature around pre-clinical CBD inhalation PK, though much more research is needed to fully characterize the PK and safety impacts of high dose CBD inhalation.

P009

CANNABIDIOL REDUCES EXTRACELLULAR LEVELS OF GLUTAMATE IN HIPPOCAMPUS OF RATS WITH TEMPORAL LOBE EPILEPSY

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Rationale: Temporal lobe epilepsy (TLE) is associated with increased hippocampal extracellular levels of glutamate, both in ictal and interictal stages. Experimental evidence points out that cannabidiol (CBD) decreases glutamate release in a rat model of seizures induced by cocaine. The aim of this study was to investigate if CBD reduces the hippocampal extracellular levels of glutamate in a rat model of TLE. **Methodology:** Male Wistar rats previously submitted to pilocarpine-induced status epilepticus were used. Animals underwent a stereotactic surgery to implant a guide-cannula in the left-ventral hippocampus once we confirmed that they presented spontaneous seizures (15 ± 2.22 days after status epilepticus). One week after surgery, rats were subchronically treated with CBD (200 mg/kg orally, TLE-CBD group, n=7) or its vehicle (9.5 mL/kg, TLE-Vh group, n=7), daily for 7 days. The results obtained were compared with those from the control group (Sham-Vh, n=7). Next day after the end of the treatment, rats were used to determine extracellular levels of glutamate in hippocampus by microdialysis experiments. Glutamate was quantified in perfusates by HPLC. **Results:** The extracellular concentration of glutamate in hippocampus of the Sham-Vh group was 1.22 ± 0.31 μM. On the other hand, glutamate concentration in TLE-Vh group was 457.10 % higher compared to Sham-Vh ($p<0.05$). Interestingly, the glutamate concentration in hippocampus of TLE-CBD group was significantly lower when compared to TLE-Vh group (74.86%, $p<0.05$), and similar to Sham-Vh group ($p=0.99$). Considering that rats from TLE-Vh and TLE-CBD groups did not present seizures during the microdialysis experiments, the results obtained represented the extracellular levels of glutamate during the interictal period. **Conclusions:** Subchronic treatment with CBD in animals with TLE reduces interictal-extracellular levels of glutamate in hippocampus. Further experiments are essential to determine if this effect is associated with reduced neuronal damage and glutamatergic excitotoxicity. **Founding:** This study was supported by the National Council of Science and Technology (CONACyT, scholarship 753802 to CMA and grant A-S3-26782 to LR) and by the pharmaceutical industry (RSHO-X™, HempMeds PX, LLC, USA).

P010

MEDICAL CANNABIS IN THE ELDERLY POPULATION

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Background: As MC becomes a more popular treatment option for chronic disorders, it is important to address its effect on the rapidly growing older population, as 80% of older adults have at least one chronic disease. Study **Methods:** A retrospective analysis was conducted using patients over the age of 75, who had used MC for at least one month through the NYS Medical Marijuana Program. **Results:** Two hundred and four patients (75=male 129=female) aged 81±6 were included in the study, and 34% reported AE on their maintenance dose. The most common AE were somnolence (13%), disequilibrium (7%), and GI disturbance (7%). Euphoria on the maintenance dosage was the uncommon, affecting only 3% of patients. AE that resolved after a change in dosage, were present in 13% of the population. The majority of patients (69%) appreciated some symptomatic benefit while on MC, with the most common being relief in chronic pain (49%), sleep (18%), neuropathy (15%), and anxiety (10%). MC was well tolerated with only 7 patients (3.4%) discontinuing due to AE. Almost a third of the patients on opioids at the initiation of MC treatment (32%) reported a decrease in opioid use. Discussion/ **Conclusion:** This study finds that MC is a well-tolerated treatment for multiple diseases in patients over the age of 75. A 1:1 tincture was the most commonly reported dosage used among patients who reported no side effects on their maintenance dosage, and some efficacy was seen in 69% of patients. Future randomized placebo controlled studies will be needed to verify the severity of side effects, as well as optimal dosing for efficacy.

P011

CAROTENOIDS AND CANNABINOIDS: AN INNOVATIVE ANTI-INFLAMMATORY COMBINATION

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Phagocytic cells have an important role in host defense against pathogens. When dysregulated they release high levels of pro-inflammatory mediators and participate in the pathogenesis of a variety of diseases, including neurodegenerative diseases. A common strategy for treating inflammation-associated diseases is based on suppressing the production of inflammatory mediators. Carotenoids and their metabolites, in addition to their direct scavenging capacity have been shown to modulate oxidative stress through several intracellular pathways and the combination of carotenoids with rosemary extract has been reported to reduce biomarkers of inflammation. Phytonutrients from hemp, including cannabinoids, terpenes, and flavonoids are multifunctional and known to have an entourage effect. Since tomato lycopene and other carotenoids are typically consumed as part of a mixed diet at levels that are too low to exert a physiological effect, we hypothesized that by combining carotenoids with cannabinoids the efficacy of the anti-inflammatory activity would be enhanced. We studied the synergistic effects of tomato lycopene and CBD on the reduction of specific inflammatory response outcomes in peritoneal macrophages and microglia. Addition of Lycopene or CBD to stimulated macrophages or microglia caused a dose dependent inhibition in nitric oxide (NO) and tumor necrosis factor alpha (TNF-α), production. When 1 uM Lycopene was added with 0.1 uM CBD a significant synergistic inhibition of NO and TNF-α production was shown in both stimulated macrophages and microglia where the inhibitory effect was increased by 6-fold. Such new products, combining phytonutrients from hemp and tomatoes offer a new approach for prevention of inflammation and portray the unique potential of a synergistic effect. This enables the use of lower doses of the active ingredients, achieved in the range of their human plasma levels upon dietary supplementation, while the combined effect is significantly stronger.

P012

MEDICAL CANNABIS IN THE TREATMENT OF NEUROPATHY

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Objective: To evaluate the efficacy and adverse effects of medical cannabis (MC) in the treatment of neuropathy Background: According to the National Institutes of Health, more than 20 million Americans suffer from neuropathy. With MC now legal in 37 states, MC presents as an anti-inflammatory and neuroprotective agent that may help in treating neuropathy and associated symptoms. **Design/Methods:** This retrospective chart analysis was conducted on patients with neuropathy as diagnosed by a board-certified neurologist in a comprehensive, neurologic outpatient setting in New York State. All patients were subsequently certified to use MC as part of New York State's Medical Marijuana Program. **Results:** 503 (247=male, 255= female) patients aged 22–99 years with neuropathy were included for this analysis. 85.1% of the study population reported benefit from using MC, with 82.5% percent of patient population (n=415) reporting a decrease in neuropathic pain/symptoms. 77.3% of the study population was able to achieve these results using only one MC product. The majority of patients used MC in tincture form (77.1%), with ratios of 20:1 (THC:CBD) and 1:1 (THC:CBD) representing 79.5% of MC products. Average daily exposures to THC and CBD were 27.2mg and 19.4mg respectively. We found that 28.0% (n=141) of the population reported side effects which were generally mild in nature. The most commonly reported side effects were fatigue (n=29), increased appetite (n=24), drowsiness (n=20), and dizziness (n=19). Less than 1.0% (n=2) chose to stop MC treatment due

to side effects. No severe AE were reported. **Conclusion:** MC as a part of a comprehensive neuropathic pain care is well tolerated and may play a role in advancing conventional care plans. The most common MC ratios used to achieve such results were 20:1 (THC:CBD) and 1:1 (THC:CBD). Further investigations, including randomized placebo-controlled trials are needed to confirm these promising results in the treatment of neuropathy. **Study Supported By:** The Harry Dent Family Foundation.

P013

OPTIMAL TREATMENT WITH CANNABIS OILS VIA ENRICHMENT WITH SPECIFICALLY SELECTED MONOTERPENES AND MONOTERPENOIDS

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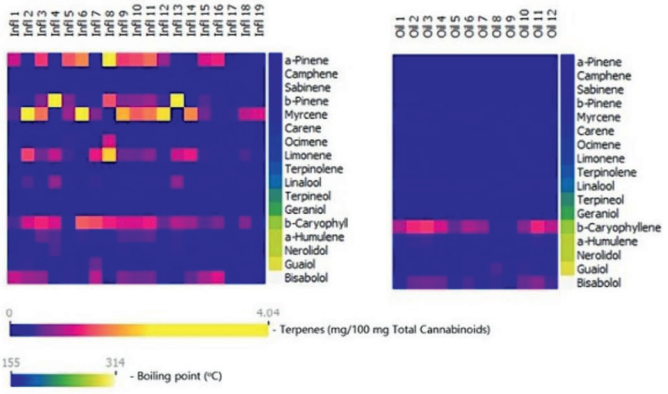
Introduction: Unfortunately, smoking is preferred over extracts (cannabis oils) among medical cannabis patients, despite its obvious drawbacks for medicinal care, including health-threatening issues, short-lasting effect, inaccuracy and poor reproducibility. This study suggests a composition-related reasoning for extracts' deficiency and methods for overcoming them. **Methods:** Changes in cannabinoids and terpenes contents during the various steps of production, including inflorescences' drying, curing, extraction and decarboxylation were analyzed. Compositions of commercial cannabis inflorescences were compared to those of commercial extracts, including inflorescences and decarboxylated extracts produced from them. **Results:** While cannabinoids content in commercial inflorescences and extracts is controlled and preserved, a significant loss of terpenes is evident in extracts, mainly of the more volatile monoterpenes and monoterpenoids. This loss changes the total content of terpenes, the proportion of monoterpenes out of the total terpenes content and the monoterpenes/cannabinoids ratio. It also essentially eliminates important differences between various extracts, e.g., those extracted from Sativa vs. those extracted from Indica chemovars. **Conclusions:** Cannabis extracts deficiency in terpenes, particularly in monoterpenes, may hamper the entourage effect, impair their pharmacological efficacy and stand in the basis of patients' preference toward smoking inflorescences. The resulting losses, questions the validity of terms such as "whole plant" and "full spectrum" extracts and contrasts the assumption that extracts represent the pharmacological profile of the inflorescences used to produce them. Furthermore, it reduces the diversity in extracts. Enriching cannabis extracts with terpenes, provides a suitable solution. Terpene-enriched extracts provide a safe, precise, reproducible, long-lasting-effect drug with full cannabinoids and terpenes content. Enrichment with selected terpenes based on terpenes' own pharmacology effects and their interaction with cannabinoids, independent of those in the original plant, paves the way for tailor-made extracts, adjusted for various medicinal aims and for needs of varying populations.



Terpenes content in commercial cannabis inflorescences and cannabis oils marketed in Israel, presented as milligrams of each terpene per 100 mg total cannabinoids content.

P014

CANNABIDIOL PRETREATMENT AVOIDS THE SHORT- AND LONG-TERM HIGH EXTRACELLULAR RELEASE OF GLUTAMATE SUBSEQUENT TO A SEVERE TRAUMATIC BRAIN INJURY

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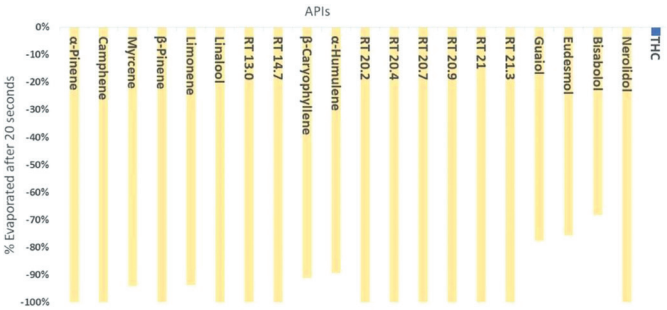
Rationale. Strategies to prevent the short- and long-term consequences induced by traumatic brain injury (TBI) are prompted. On the other hand, cannabidiol (CBD) is a multitarget molecule that induces neuroprotection and reduces excitotoxicity in animal models. The present study focused to demonstrate that pretreatment with CBD lessens the high extracellular levels of glutamate, short- and long-term after a severe TBI. Methods. Male Wistar rats (250–300 g) were used. A) Short-term effects. Rats previously implanted with a guide-cannula in sensorimotor cortex were pretreated with CBD (50, 100 or 200 mg/kg p.o. daily for 7 days, n=7 per dose), or vehicle (n=7). Twelve hours after the last administration, animals were used for microdialysis experiments. Under isofluorane anesthesia animals received a lateral fluid percussion injury to induce a severe TBI. Dialysates were continuously recovered before, during and after TBI. The results from this experiment were used to determine the optimal dose of CBD, i.e., the dose more effective to lessen the high glutamate release after TBI. B) Long-term effects (n=21). Rats were pretreated during 7 days with the optimal dose of CBD or vehicle (n=7 per group). Animals were anesthetized and submitted to a severe TBI 24 h after the last administration. Twenty-three days after TBI-induction, rats were used for microdialysis experiments (see above). The dialysates were evaluated by HPLC to determine glutamate concentrations. Results. A) Short-term experiments. TBI group showed an increased glutamate concentration 30 min post-TBI (1402%±331 $p<0.01$ vs SHAM). CBD at 100 mg/kg reduced the TBI-induced

glutamate release (468%±128 p<0.05 vs TBI). This effect was not evident with CBD at 50 or 200 mg/kg. Then, 100 mg/kg was established as the optimal dose. B) Long-term experiments. TBI group showed a higher glutamate concentration (1.8±0.28 μM, p<0.05 vs SHAM group). In contrast, the glutamate concentration of the group pretreated with CBD (100 mg/kg) was lower than TBI group (0.72±0.20 μM, p<0.001) and similar to SHAM group (p=0.6195). Conclusions. The present study supports that subchronic pretreatment with CBD may represent a therapeutic strategy to prevent glutamatergic excitotoxicity in individuals with high risk of experiencing a severe TBI.



Percentage of THC and terpenes evaporated during 20 seconds of vaporization. As seen, while only 13% of the THC present was evaporated, terpenes had gone through full or mostly full evaporation.

P015

NON-SYNCHRONOUS EVAPORATION OF CANNABIS' ACTIVE INGREDIENTS – POTENTIAL IMPLICATIONS FOR SMOKING AND VAPING THE MEDICAL CANNABIS DRUG

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Introduction: Too little is known about the actually consumed doses of active pharmaceutical ingredients (APIs) on administering medical cannabis via vaping and smoking. In both, APIs are evaporated and inhaled. Medical cannabis products contain dozens of APIs, which differ markedly in their boiling points and vapor pressures at the relevant temperatures of operation, with important potential implications. **Methods:** Ground medical cannabis inflorescences were treated in a commercial vaporizer at several temperatures and for various durations. Medical cannabis cigarettes were "smoked" to various extents (e.g.one third, three quarters) in a device simulating human smoking. Samples of the initial composition and of the residues were analyzed for their cannabinoids (HPLC) and terpenes content (GC). **Results:** Contrary to data in multiple publications, the actual boiling points of the cannabinoids are about 450ºC, much higher than those of a vaporizer operation. Yet, fractions of the cannabinoids do evaporate (after decarboxylation), depending on operating temperature and duration. The degree of terpenes evaporation is greater, but differs significantly according to the terpenes vapor pressures at the operating temperature. In smoking, the picture is further complicated by temperature changes along the cigarette and by the fact that, typically, only a fraction of the cigarette is consumed each time. **Conclusions:** The compositions actually administered in vaping and smoking may markedly differ from those of the used cannabis formulation. The inhaled vapors have larger monoterpenes to cannabinoids ratios with important implications for the medical effect. Furthermore, large fractions of the volatile terpenes are received before significant amounts of cannabinoids evaporate. In smoking, the composition inhaled during the first half of the cigarette may markedly differ from that of the second half. Knowledge of the vapor pressure of the various APIs and its dependency on temperature, helps in predicting the inhaled composition and in selecting the preferred conditions.

P016

CYTOTOXIC ACTIVITY OF Δ9–TETRAHYDROCANNABINOL (THC)-RICH COMPOSITIONS FROM CANNABIS AGAINST OVARIAN CANCER CELLS AND THEIR SYNERGY WITH NIRAPARIB

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Ovarian cancer (OC) is the most lethal gynecologic malignancy in the western world. Most of cases are diagnosed at an advanced stage. Cannabis sativa is widely used to alleviate numerous symptoms associated with medical conditions and recently, a large number of studies demonstrated that phytocannabinoids have anti-cancer activity in vitro and in vivo. Yet, only a few studies have examined the effect of cannabis compounds against OC. Furthermore, a plausible approach for treatment of OC patient suggest to combine the cannabis-based treatment with chemotherapy. We examined the efficiency of combinations of cannabis compounds against OC and the effect of co-treatment of these cannabis compounds and niraparib, a PARP-inhibitor chemotherapy drug. A high Δ9–tetrahydrocannabinol (THC) cannabis strain extract was divided into fractions. The fractions were analyzed and their content was reconstituted for the composition of phytocannabinoids using standard mix (SM). Cytotoxic activity was determined by XTT assay on HTB75, HTB76 and HTB161 high-grade serous OC cell lines. Apoptosis and cell cycle were determined by fluorescence-activated cell sorting (FACS). Cell migration was determined by scratch assay. Gene expression was determined by quantitative PCR. Two active fractions were identified, F5 and F7. The fractions and SM showed cytotoxic activity against OC cells; they decreased cell viability and cell motility. The most effective phytocannabinoid combination was THC+cannabichromene (CBC)+cannabigerol (CBG). The fractions affected cell cycle by increasing G2/M or S arrest, led to cell apoptosis and to a marked reduction in cell migration. F7 and F5 acted in synergy with niraparib and were ~50 fold more cytotoxic to OC cells than to normal

cells (keratinocytes). Niraparib+F7 combined treatment was cytotoxic to OC cells isolated from patient's lymph node. These cells showed only low sensitivity to niraparib treatment. The synergistic co-treatment by niraparib+F7 markedly reduced tumor size in xenograft mice model. In addition, niraparib+fraction (F5 and F7) treatments reduced Mitogen-Activated Protein Kinase 4 (MAPK4) gene expression; this reduction may act in synergy with PARP inhibition activity. Cannabis compounds and their combinations with niraparib should be examined for efficacy in clinical trials.

P017

TRISSOMY 21 AND LENNOX-GASTAUT SYNDROME: A REPORT OF IMPROVEMENT AFTER CANABIDIOL USE

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Case Presentation E.V.S., currently aged 3 years and 1 month, had her first appointment at the Difficult Control Neuropediatric Epilepsy and Ketogenic Diet outpatient clinic of Centro Universitário ABC in November 2020. She was referred by a pediatrician due to her difficult-to-control multifocal epilepsy and Trisomy 21. She started with spasms in the upper limbs and hypertonia in the lower limbs at 5 months of age, presenting 20 to 30 crises a day. She started outpatient follow-up at 9 months, when diagnosed with West Syndrome. She arrived at our service at 2 years and 5 months, weighing 10.25 Kg and measuring 82 cm. She was using valproic acid 48.7 mg/kg/day, levetiracetam 58.5 mg/kg/day and clobazam 0.73 mg/kg/day. At this moment without control of the convulsive crises. She had partial cephalic support, sitting unsupported for a few seconds. Discussion Patient undergoing monthly follow-up. Being evaluated both from the diary of crises point of view as the nutritional status and neuro-psychomotor development. Drugs were adjusted to sodium divalproate and levetiracetam, and we started using cannabidiol (6000 mg, 100 mg/ml <0.3% THC) 5 drops every 12 hours at 2 years and 10 months. 4 days after the start of cannabidiol, the mother did not notice any new seizures, showing control of the epilepsy since then. Nutritional interventions carried out over the past 8 months consisted of introduction of new foods from the vegetables group, varying among them to develop palatability; changing the consistency of the diet to a pasty consistency to facilitate swallowing; fractionation of the diet at each appointment; hypercaloric and hyperprotein nutritional supplementation. She showed a significant improvement in sleep, stopped grinding her teeth during sleepiness, becoming more attentive, with more facial expressions and with improved learning, swallowing, food acceptance, interaction and head and trunk support. A major pillar for the treatment and monitoring of this patient is the family's constancy and persistence in following the guidelines of both teams. Final Comments The patient presents a gradual improvement in neuro-psychomotor development with follow-up with the Nutrition team from our clinic, in addition to a significant decrease in seizures after the introduction of cannabidiol.

P018

EFFICIENT NEBULIZABLE CANNABINOID CARRYING CONTROLLED RELEASE SUSPENSIONS AND FORMULATIONS.

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THE PROBLEM: LOW BIOAVAILABILITY OF INHALED CANNABINOIDS. Use of inhalers for delivery of nebulized APIs such as cannabinoids into the bloodstream is hindered by unsatisfactory cannabinoid bioavilability of 20-40%. Physicochemical barriers to efficient absorption at the pulmonary alveoli must be overcome in order for the inhaled cannabinoids to reach the alveoli in sufficient quantity for optimized uptake of the delivered drug. Small nebulized droplets < 200 nm carrying the cannabinoids do not adhere to the alveoli and are exhaled into the atmosphere. Large nebulized droplets 1600> nm are deposited much higher up in the respiratory tract. They do not reach the alveoli target tissues and therefore the cannabinoid quantity is not absorbed at the alveolar site. SOLUTION API carrier formulations are configured for inhalation by nebulized administration. Formulations provide cannabinoid medicaments for delivery to the body via the mucosal surfaces of the respiratory system for systemic distribution. The unique formulations include an amphiphilic lipid carrier in the form of a colloidal composition. The suspensions include aggregates or micelles in a continuous aqueous phase and Cannabinoid API. The amphiphilic lipid carrier has high adhesiveness to mucous membranes within the respiratory system. The lipid carrier has a high load capacity for transport of active cannabinoids. These formulations carry a large amount of active agent for controlled and prolonged release at the mucous membrane surfaces and surrounding tissue. The lipid – cannabinoid particles are optimized to be included in the size specific aerosol droplets most appropriate for efficient delivery to alveoli. The formulations provide optimal suspensions for inhalation applications. The cannabinoids are held by the carrier through hydrophobic interactions. The API cannabinoid is packaged in the lipid like carrying particle. The lipid – cannabinoid particle is enveloped in the aerosol carrier droplets. 90% of the lipid – cannabinoid particles are contained in aerosol carrier droplets characterized by Optimal size distribution for reaching the alveoli walls with minimal deposition in the Upper Respiratory Tract. Optimal composition to adhere temporarily to the alveoli walls Contains Lipid – cannabinoid particles Lipid – cannabinoid particle releasing cannabinoid across the alveoli-blood membrane thereby providing high bioavailability of the inhaled cannabinoid.

POSTER PRESENTATIONS

02. BIZ: New Technologies, New Opportunities

P019

TRANSFORMING ACADEMIC EDUCATION AND RESEARCH AROUND CANNABIS LEGALIZATION, MEDICAL-USE CANNABIS, AND SOCIAL EQUITY IN NEW JERSEY

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Background: In November 2020, 67% of New Jersey (NJ) residents voted yes to legalizing the adult use of cannabis. In 2019, 48% of all admissions to NJ substance abuse treatment centers were for opioids (Substance Abuse Statewide Report, 2020). From Sept-Dec 2020, Rider University, CannabisBPO, and the Cannabis Center of Excellence taught an Undergraduate course on cannabis legalization and conducted a research study together with the students as part of the course. Methods Dr. Trocchio (Rider University) and Dr. McNabb (CCOE); Marshall Ogen (CannabisBPO); and Shekia Scott (Senior Cannabis Expert) served as Principal Investigators with Rider University IRB approval on a research study of NJ residents 21+ years asking opinions about legalizing adult-use cannabis, personal cannabis use, and social justice issues. A survey was developed and disseminated via Survey Monkey using a convenience sampling approach from 09/30/2021 to 11/03/2021. Outreach included: social media platforms, email, veteran associations, and NJ cannabis dispensaries. Results were analyzed using R statistical software. Results A total of 240 adults (ages 18+) responded and 90% were in favor of legalizing adult-use cannabis; 85% felt it would positively affect the economy. Nearly half (40%) reported consuming cannabis, 53% were non-cannabis consumers and 7% did not want to disclose. Of those who consume cannabis, 54% reported for adult use only, 32% used cannabis for medical purposes only, and 11% consumed both medically and for adult use. Cannabis was reported helpful for anxiety (70%), depression (55%), pain (35%), and insomnia (42%). The most common unwanted side effects included dry mouth (50%), changes in appetite (40%); and more or less talkative (32%). Cannabis was also reported to be used to reduce unwanted medication or opioid use (see Table 1). Discussion This type of cannabis academic educational model is the first of its kind in cannabis, teaching while also conducting a relevant and real-time research study as part of coursework. Study findings reveal NJ cannabis consumers and patients are utilizing medical cannabis to replace or reduce medication or opiate use. More research and educational programs surrounding this topic should be conducted.

Table 1. 2020 NJ Survey Respondents who Reported Reduction in Medication Use with Cannabis Consumption

Indicator	Percent of Study Respondents N=240
Actively Reducing Prescription Meds with Cannabis	23%
Reduction in Opiate Use	9%
Reduction in Over the Counter Medications	24%
Cannabis helps avoid starting other medicines (including opiates)	19%

POSTER PRESENTATIONS

03. AGR: Advanced Agriculture and Production

P020

CAN CARBON DOTS INCREASE SECOND METABOLITES LEVELS IN CANNABIS? A SOLID HYPOTHESIS

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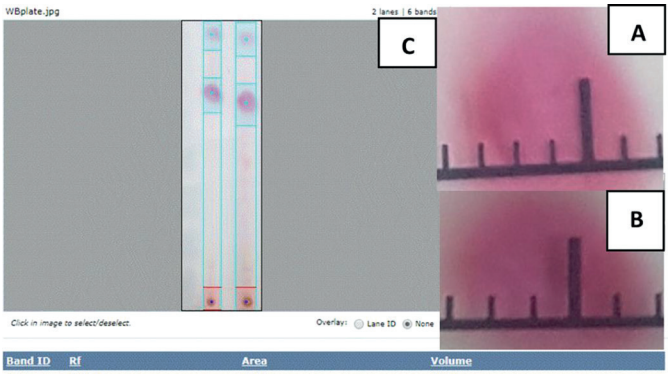
Introduction: Carbon Dots (CD) are nano particles produced by different inputs, like waste [1]. Nano materials are used in agriculture substituting and/or boosting fertilizers [2]. The CD literature is limited treating positive and negatives effects [3]. One of the positive effects may be adenosine triphosphate (ATP) stimuli, being that CDS are promoter of plant growth [4]. Method: This experiment used seven CD doses of 100 mg/liter during cultivation of White Berry Cannabis Strain. ABRACAM cultivated indoor 16 plants using the same nutrients and light. CD was applied foliar using 15 days intervals in 8 plants. Federal University of Piauí (UFPI) professors tested four flower samples using Thin Layer Chromatography (TLC)[5,6] being two samples cultivated with CD and two samples of plants with no CD treatment. To validate TLC readings ABRACAM sent a Cannabis extract sample to Federal University of Rio Grande do Norte (UFRN) test using High-Pressure Liquid Chromatography (HPLC). After comparison we concluded that errors between TLC and HPLC can range from -0,645% and 1,01% when professionals, as professors, run the test and analysis. The tetrahydrocannabinol (THC) levels at first analysis were 8,4% for the control sample and 8,85% for the sample with CD (Figure 1 A and B). An 5,35% increase in THC levels (8,4*100/8,85). A second software analysis by JustQuantify [7] measured the volume of each sample at the silica plate. Results indicate that sample that used CD (Rand ID 2_2 at figure 2) had 24% more volume (569,37*100/459,16) than the one that did not use CD (Rand ID 2_1 at Figure 2). Conclusion: TLC is not the



Band ID	Rf	Area	Volume
1_1	0.952	6200	155.4
1_2	0.749	7440	459.16
1_3	0.032	4836	191.81
2_1	0.934	8352	170.41
2_2	0.717	10368	569.37
2_3	0.03	5760	231.71

Fig. 1. Cannabinoid percentage ruler and from JustQuantify.

standard for the Cannabis industry, but it can raise valuable hypotheses about promoting second metabolites as THC. This article used a double validation analysis indicating an increase in THC levels, from a percentage ruler (5,35%) and a software (24%). These results may indicate that CDs are a possible cannabinoid booster.

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P021

PREDICTION OF PHYTOCANNABINOID AND TERPENE CONCENTRATIONS IN CANNABIS INFLORESCENCE USING NEAR-INFRARED SPECTROSCOPY AND CHEMOMETRICS

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Cannabis inflorescence are widely used for various medicinal conditions. Although considered as medicinal grade product, there is a lack of standardization and reproducibility in terms of steady concentrations of phytocannabinoids and terpenes between inflorescences from the same cultivar. At the present, phytocannabinoids and terpenes within the cannabis inflorescence are quantified using highly expensive and time consuming instrumentations such as high liquid pressure chromatography (HPLC) and/or gas chromatography (GC) which require trained personnel. Our study aims at replacing these quantification methods with a fast and cheap quantification analytical method using near-infrared spectroscopy coupled with multivariate statistical methods. Multivariate calibration techniques such as partial least squares (PLS) are often employed to predict concentrations of major secondary metabolites in various plants under well-defined growing conditions. We have utilized these techniques by establishing an extensive database of cannabinoid and terpene content of 15 different locally grown Cannabis cultivars. Our results revealed high R^2 of both calibration and cross validation datasets, with low root mean square error ratio for numerous neutral and acidic cannabinoids as well as major terpenes (Figure 1). Our results may form the foundation for the development of a cheap and rapid quantification tool for growers and consumers.

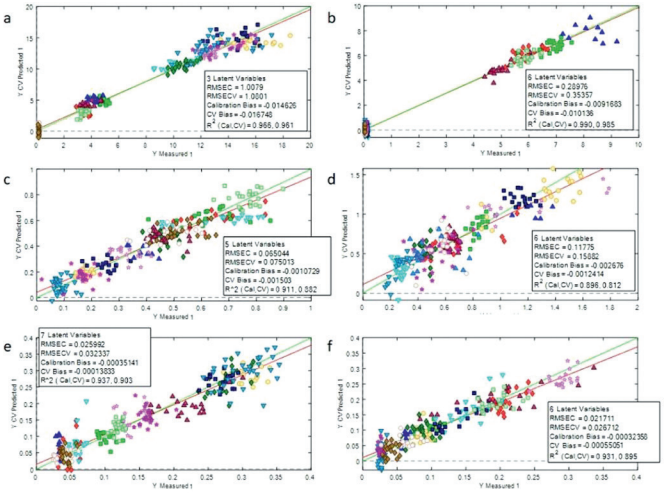

Fig. 1. Cross validation correlations between the measured concentrations (in wt%) of (a) THCA, (b) CBDA, (c) CBCA and (d) CBGA by HPLC, (e) -Caryophyllene and (f) -Myrcene by GC and predicted concentration using PLS-R model of near IR spectra.

P022

ANALYSIS OF MAIN ACTIVE SUBSTANCES IN DIFFERENT HEMP (CANNABIS SATIVA L.) PHENOTYPES

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Cannabis populations can often have a relatively high heterogeneity with different phenotypes and chemical profiles despite being from the same variety. Little information exists about cannabinoid / terpenoid profiles and polyphenol content in different hemp phenotypes within the same variety. For this study, 11 phenotypes from three different varieties ["Carmagnola" selected (CS), "Tiborszallasi" (TS), and "Finola" selection (FS)] were analyzed. The components of essential oil (29) were determined using gas chromatography with flame ionization detection (GC/FID), and 10 different cannabinoids were analyzed using high-performance liquid chromatography (HPLC). Principal component analysis (PCA) and analysis of variance (ANOVA) showed that according to the components of essential oil, FS and TS plants were more uniform than CS plants, where great differences between CI and CII phenotypes were found out. The content of cannabinoid CBD-A was the highest in all four FS phenotypes (up to 6.59 %). By comparing cannabinoid profiles, FS was clearly separated from TS and CS, while these two varieties were not clearly distinguishable. Phenotypes TV and CI had the highest total content of Δ-9-THC-A (1.39 % and 0.91 % respectively), while all phenotypes of FS had the highest total content of CBD (up to 0.78 %) and THC (up to 0.11 %). Furthermore, total polyphenol content (TPC) and antioxidant activity in female inflorescences were determined in six selected phenotypes of three investigated varieties. Two different extraction solvents were used: distilled water and ethanol (98%). TPC was measured using the Folin-Ciocalteu's reagent, and antioxidant activity was determined using DPPH reagent. In ethanol extracts, the highest analyzed TPC was in the phenotype FIV (31.8 mg GAE/g) and the highest antioxidant activity was determined in the FII phenotype (75.3 % of DPPH radical inactivation). In water extracts, the highest TPC was evaluated in the FII phenotype and the highest antioxidant activity was detected in CII and TIII phenotypes. TPC and antioxidant activity analysis both showed that ethanol extracts yielded better results. Obtained results are useful for the development of new supplementary ingredients, for different pharmacy treatments, and for further breeding purposes.

P023

PAVING THE ROAD TO CANNABIS/HEMP STANDARDIZATION: MODERN AND NEW BREEDING TECHNOLOGIES (NBT'S) ACCELERATING CANNABIS VARIETY DEVELOPMENT AND EFFICIENT CULTIVATION

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Although Cannabis has been found to be one of the oldest domesticated crops, it is currently lagging behind other agricultural crops in terms of implementing modern breeding practices and new breeding technologies (NBT's), mainly due to its global legal status throughout the 20th century. In addition to hampering scientific development, the Cannabis plant's illegality resulted in growers adopting inadequate cultivation practices such as vegetative propagation through clones cut from a mother plant. While cloning aims to ensure genetic identity (true to type), in the long run, it achieves the complete opposite. Product inconsistency growers are facing today is largely due to issues arising from cloning practices. Three major reasons can be listed: 1. As mother plants (soil grown or from tissue culture) age, mutations accumulate and are passed on to new clones and these new mutations are fixed in the population. 2. Clone performance is dependent on the mother plant's age. Clones cut from a one-month-old mother will not perform as clones cut from an 18-month-old mother. 3. Eventually, variation in clone performance forces the grower to replace the mother plant, thus, changing its genetic identity and assuring loss of product consistency. Eliminating the need of using mother plants and clones by shifting to sexually produced seeds as propagating material is an essential step for the industry. BetterSeeds (formerly CanBreed) has developed seeds that are true F1 hybrids created from crossing stable parental lines, thus, assuring that all progeny produced from a single cross are genetically identical. Over time, cultivation based on hybrid seeds will allow maintaining product consistency as well as reducing logistical costs (eliminating the need for dedicated mother plant plantation and clone's nursery). Development of novel agricultural traits can be achieved by using CRISPR based genome editing. In addition to accelerating the breeding process while achieving high accuracy it also saves significant time and resources compared to other breeding tools available today. BetterSeeds' genetic traits and accomplishments in gene editing will be discussed. To summarize, we envision a bright future for Cannabis breeding and cultivation, enabled by seeds and genome editing.

Medical Cannabis and Cannabinoids

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