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ABSTRACTS BOOK

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ORAL PRESENTATIONS

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Stoned and rejected: a naturalistic study of the impact of social exclusion and acute cannabis use on sexual arousal, sexual inhibitions and risky sexual behavior

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Background: Pain Overlap Theory predicts that because cannabis numbs physical pain, it should also numb people to the aversive effects of social rejection and loneliness. Nonetheless, cannabis use may also increase social pain associated with stigma, compromised health and risky sexual behavior, as it is correlated with a higher number of sexual partners, multiple partners, and a lower use of condoms. Aphrodisiac effects of acute cannabis have been frequently promoted, but contradictory data has been accumulated regarding chronic use and gender differences.

Objective: To explore the effect of cannabis use, experimentally induced social rejection, and gender on sexual arousal, sexual inhibitions, and risky sexual behavior.

Methods: Fifty-five heterosexual frequent cannabis users (Mage=29.8; 48% females) were randomly exposed to an online real-time ostracism (or social inclusion) manipulation while they were acutely intoxicated by their own chosen smoked cannabis. Next, they rated their willingness to engage sexually with unknown partner/s and reported about sexual arousal and sexual inhibition.

Results: Accepted women and rejected men report increased sexual motivation and arousal while under the influence of cannabis. Both socially rejected women and socially accepted men report lower sexual inhibitions. Whereas rejected women report a higher willingness to engage sexually with an unknown partner while intoxicated, rejection lowered these ratings among intoxicated men. Thus, the combined impact of cannabis and social exclusion increases sexual restraints among men, yet enhances impulsivity among women: decreasing inhibitions and exacerbating risky behavior, without affecting sexual desire or motivation.

Discussion: Findings indicate that gender and rejection interact to predict sexual behavior among cannabis users, adding to a sparse literature about cannabis` impact on sexual behavior and risk-taking. Understanding potential individual and public health consequences by focusing solely on either factor may not suffice. Implications for future research, prevention, and treatment are discussed.

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Questioning Assumptions about the Abuse Potential of Medical Cannabis and Cannabinoids: A Critical Review and Rationale and Focus for Clinical Trials

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Background
While a rapidly growing literature focuses on efficacy in specific applications of medical cannabinoids, safety is not clear and much less well reported. Characteristics of the ever-increasing mass of data on cannabis and a limited number of cannabinoids are data of mixed quality, inconsistent results, and contradictory evidence for the questions being addressed.

Objectives
We address the issue of abuse potential or liability by examining representative research data for validity and generalizability and conclude that there are a set of tacit assumptions that underlie much cannabis research and constitute threats to the validity of data collection and conclusions derived from that data, especially in the area of abuse liability. These admittedly broad assumptions include (a) a standard cannabis formulation, (b) standard routes of administration, standard potency dosing, (c) a standard pattern of use, (d) a standard user or patient, and (e) a standard vulnerability to misuse or dependence. Thus, our purpose was to identify gaps and densities in the evidence and opinions reported in an evolving literature to justify and design clinical trials in the area of abuse potential of medical cannabinoids.

Methods
We followed the scoping review methodological framework and guidelines proposed by Arksey and O'Malley (2005), and the Joanna Briggs Institute (Peters et al 2015) as well as suggestions offered by Tricco and colleagues (2016). Seven electronic databases [Google Scholar, Scopus, Web of Science, Embase, PubMed/MEDLINE, CINAHL, and the Cochrane Library] were searched to identify English-language peer-reviewed publications published generally within the last 20 years.

Results
Unpacking and questioning these assumptions lead to the conclusion that far more rigorous language and research design are needed to definitively address the question of cannabis abuse potential.

Conclusion
Based on the best available evidence, the abuse liability of medically supervised cannabis is comparable to any other class of pharmaceutical agents.

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"Flower Power": Controlled Inhalation of Chemotype I Cannabis Flos Improves Health-Related Quality of Life and Alleviates Symptoms of Chronic Pain and Anxiety in UK Patients

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Background: In November 2018, the UK's Home Office established a legal route for eligible patients to be prescribed cannabis-based products for medicinal use in humans (CBPMs) as unlicensed medicines. These include liquid cannabis extracts for oral administration ("oils") and dried flowers for inhalation ("flos"). Smoking of CBPMs is expressly prohibited. To date, chemotype I (THC-predominant) cannabis flos remain the most frequently prescribed CBPM in project Twenty21 (T21), UK's first multi-center, prospective, observational cannabis patient registry.

Objective: To characterize patient-reported clinical outcomes associated with the controlled inhalation of chemotype I cannabis flos in a cohort of treatment-resistant, chronically ill patients.

Methods: This observational, prospective study analyzes patient-reported outcome measures (PROMS) collected by T21 associated with the inhalation of Khiron HK 20/1, the most prescribed CBPM in the project. PROMS collected at baseline and at subsequent follow-ups included health-related quality of life (HRQoL), general mood, and sleep. Condition-specific measures of illness severity were performed with the Brief Pain Inventory Short Form (BPI-SF) and the Generalized Anxiety Disorder 7-Item Scale (GAD-7).

Results: Participants (N=344) were mostly males (77.6%, average age = 38.3) diagnosed primarily with chronic pain (50.9%) and anxiety-related disorders (25.3%). Inhalation of Khiron HK 20/1 was associated with a marked increase in self-reported HRQoL, general mood, and sleep (N=344; P0.001). Condition-specific assessments showed significant improvements in pain severity (T=6.67; P0.001) and interference (T=7.19; P0.001) in chronic pain patients (N=174). A similar symptomatic alleviation was reported by patients diagnosed with anxiety-related disorders (N=107; T=12.9; P0.001).

Conclusion: Controlled inhalation of pharmaceutical grade, THC-predominant cannabis flos is associated with a significant improvement in patient-reported pain scores, mood, anxiety, sleep disturbances and overall HRQoL in a treatment-resistant clinical population.

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Phytocannabinoids and Periodontal Inflammation

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Background

Periodontitis is an inflammatory disease that affects 20–50 % of the world`s population and is considered one of the most common causes of tooth loss. In this sense, new low-molecular therapeutics are being sought that meet three criteria, namely anti-inflammatory and antibacterial effects with an acceptable safety profile. One of the currently studied groups of substances that can meet those criteria are non-psychotropic phytocannabinoids, especially cannabidiol (CBD).

Methods

At first, we preclinically evaluated the anti-inflammatory and antimicrobial effect of phytocannabinoids, CBD, cannabigerol (CBG), cannabichromene (CBC) and cannabinol (CBN). In the clinical part, placebo-control double-blind randomized study with chronic periodontitis patients was conducted monocentrically in three groups, who used an experimental toothpaste and dental gel without CBD (placebo group A, n = 30) and with 1% (w/w) CBD (group B, n = 30). Group C (as active comparator, n = 30) used placebo toothpaste without CBD and was treated with dental gel Corsodyl containing 1% chlorhexidine digluconate.

Results

At the level of preclinical findings, the effect of CBD on the suppression of inflammation and the growth of selected periodontal pathogenic bacteria was demonstrated. The effectiveness was confirmed for CBD in comparison to CBG, CBC and CBN under in vitro conditions. Based on these results, we performed clinical trial that demonstrated a statistically significant improvement in hygiene and periodontal indices after CBD application (group B) compared to the control groups A and C. The improvement in the evaluated indices in group B from 0 d to the end of CBD intervention (56 d) ranged between 20–45 %. The results also indicate that CBD will be able to modulate the oral microbial ecology, primarily by inhibiting the growth of paropathogenic bacteria such as P. gingivalis.

Conclusions

The obtained results can support further applications of CBD and other non-psychotropic phytocannabinoids in dental practice.

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The Impact of Cannabidiol Treatment on Brain Function and Metabolism of Patients with a Psychotic Disorder

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Background: Psychosis is a chronic and serious mental disorder with an urgent need for novel and more effective treatments. A promising potential new antipsychotic agent is the non-intoxicating cannabinoid compound cannabidiol (CBD). The first clinical trials with CBD treatment of psychosis patients show its ability as an effective, safe and well-tolerated antipsychotic agent. However, the neurobiological mechanisms underlying the antipsychotic profile of CBD are currently unknown.

Objectives: In this randomised, double-blind, placebo-controlled, parallel-group intervention study, we investigated the impact of 28-day adjunctive CBD or placebo treatment (600 mg daily) on brain function and metabolism of 31 recent-onset psychosis patients (5 years after diagnosis).

Methods: Before and after treatment, patients underwent a Magnetic Resonance Imaging (MRI) session, which provided the opportunity to examine impact of CBD treatment on three robust pathophysiological features of psychosis patients: 1) resting state connectivity in functional brain networks, 2) prefrontal metabolite concentrations including GABA and glutamate levels, and 3) brain activity during reward processing. Symptomatology was also determined.

Results: CBD treatment significantly changed functional connectivity in the default mode network, with increased connectivity in the CBD group. Although there were no significant treatment effects on prefrontal metabolite concentrations, we showed a different relationship of glutamate levels and psychotic symptom severity between treatment groups, with reduced glutamate concentrations associated with fewer symptoms after CBD. CBD treatment did not affect either reward brain activity or functional connectivity in executive and salience networks.

Conclusion: Adjunctive CBD treatment of psychosis patients induces changes in default mode functional connectivity, but not prefrontal metabolite concentrations or reward brain activity. Abnormal default mode connectivity underlies the experience of psychotic symptoms through its role in introspective processing. Our findings support the notion that CBD treatment attenuates impaired default mode connectivity of psychosis patients, which may be involved in the therapeutic effects of CBD.

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Novel Medical Cannabis Regimens in the Canadian Veteran Population: Reducing Negative Side Effects of Polypharmacy and Optimizing Outcomes

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BACKGROUND and OBJECTIVES: A large portion of the veteran population suffers from PTSD and chronic pain, with complex symptomatologies that are not adequately addressed by conventional treatment protocols. As such, a major issue in this complex medical population is polypharmacy. The Canadian veteran population is one of the few patient populations globally that has had ongoing access to more than 3 grams a day of medical cannabis (MC) treatment. The present study sought to determine the impact of MC treatment on polypharmacy for veterans with PTSD. METHODS: The present study made use of retrospective observational review of the MC regimens of 20 veterans (both initial and current) and pharmaceutical prescriptions prior to and after initiating MC therapy. RESULTS: Responses indicated that most veterans took upwards of 4-5 prescription medications a day causing unwanted negative side effects, prior to MC treatment, while this number dramatically decreased following the initiation of MC treatment. In fact, many veterans initiated MC treatment to decrease their reliance on other pharmaceuticals, with most completely stopping other medications after optimizing MC treatment. Moreover, results indicated that over a 5 year period (2017-2022) of MC treatment, regimens have evolved from use of dried flower primarily to a combination of dried flower, oil, and edibles, with varying percentages of CBD, THC, CBN, and various turpenes. CONCLUSION: These results reveal important real world response trends that are vital for informing future MC research and treatment protocols. Veterans reported improved physical, mental, psychosocial, and intimate partner functioning, with markedly reduced negative side effects. The results indicate that a regimen dosed above MC 3 grams a day and composed of several MC formulations is potentially a multi-purpose and effective treatment protocol that may be used to replace multiple-classes of medications, which traditionally have been used to treat physical and mental health symptoms.

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Study of Antimicrobial Activity of Hemp Extract Seed Oil against Staphylococcus Pseudintermedius and Pseudomonas Aeruginosa Strains Isolated from Pyoderma and External Otitis in Dogs

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Background: Scientific studies have shown that Hemp (Cannabis sativa) and its extracts (essential oil, seed oil and cannabinoids) possess antimicrobial properties against both Gram-positive and Gram-negative multi-resistant pathogenic bacteria and fungi. These findings make Hemp and its derivatives promising candidates for the future development of innovative, nonconventional antimicrobial therapies against pathogenic bacteria of zoonotic and veterinary clinical interest. Among these, Staphylococcus pseudintermedius and Pseudomonas aeruginosa are responsible for serious infections in dogs and, according to EFSA, they have been identified among the most relevant antimicrobial-resistant bacteria in Europe for companion animals. Objectives: The aim of this study was to evaluate in vitro the antimicrobial activity of hemp extract seed oil against Staphylococcus pseudintermedius and Pseudomonas aeruginosa isolates from canine pyoderma and external otitis, respectively. Methods: Twenty bacterial strains (10 methicillin-resistant S. pseudintermedius and 10 P. aeruginosa) were included in this work. The assessment of the antimicrobial activity of hemp seed oil was performed by broth-microdilution to determine the minimum inhibitory concentration (MIC). We tested scalar dilutions of hemp seed oil starting from a maximum value of 0.2%. The hemp seed oil used in this study was characterized by the absence of cannabidiol (CBD) and tetrahydrocannabinol (THC). Results: The hemp seed oil showed higher activity against S. pseudintermedius than P. aeruginosa. The MIC value for all S. pseudintermedius and P. aeruginosa was indeed 0.05% and 0.2%, respectively. Conclusion: CBD and THC are widely reported to be responsible for the antimicrobial capacity of hemp extracts. Our results highlight that hemp seed oil even without CBD and THC has antimicrobial properties against S. pseudintermedius. Further studies will be needed to unveil the mechanisms underlying antibacterial activity of CBD and THC free-hemp seed oil and to establish its potential as topical treatment for skin infections.

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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 ∆-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 therapy5. 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.

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Safety and Feasibility of Administration of an Oral Cannabis Preparation in The Preoperative Period in Breast and Oral Cavity Cancer

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Background- Cannabis, world's oldest cultivated medicinal plant, has potential applications in oncology, in reducing chronic pain, stimulating appetite, alleviating nausea/vomiting, improving overall well-being as well as its anti-cancer properties. A phase-1 dose escalation study is currently ongoing at our centre to determine safety of pre-operative oral cannabis in breast and oral cavity(OC) cancer.

Objectives-

Primary objective is to determine maximum tolerated dose and establish drug limiting toxicity(DLT). Secondary objectives are pharmacokinetic profiling and transcriptomic analysis of tumour tissue.

Methods-

Non-metastatic breast and OC carcinoma patients planned for curative surgery are consented after medical and mini-psychiatric evaluation. The investigational product(IP) is capsule prepared from dried leaves of C. sativa containing 2.5mg of tetrahydrocannabinol(THC) and 2.5mg cannabidiol(CBD) in 100 mg monocrotolyn oil extract. The capsules are manufactured in an Ayurvedic GMP facility. The dose escalation strategy is a classical 3+3, phase-1 design, starting with 5mg THC+5mg CBD increasing to 10, 20 and 30 mg each. Patients receive IP for 5 days with hemodynamic and psychiatric monitoring and undergo planned surgery on day-6. Pharmacokinetic samples are collected on all days at predefined time-points and plasma levels of THC, 11-OH-THC, 11-COOH-THC and CBD will be determined using a validated LC-MS/MS method. Tumour tissue is collected before 1st dose and during surgery.

Results-

Eight patients are enrolled so far (3-breast, 3-buccal mucosa and 2-tongue primaries). First 3 patients completed the study without DLT at 5+5mg dose. One patient at dose level-2 (10+10mg) was withdrawn on day-2 due to episodes of severe anxiety. All other patients completed study protocol. Common adverse effects were headache, heavy head, hypotension, epigastric discomfort, diarrhoea. One patient had grade-3 hypotension needing IV-fluids.

Conclusion-

We report the first phase-1 study of cannabis in breast and OC cancer in pre-operative setting. MTD identified will be further explored in phase-3 clinical trials for efficacy.

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Randomised, Placebo-Controlled, Double-Blind Studies of Medicinal Cannabis for Symptom Management in Patients with Advanced Cancer

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Background. Following robust public pressure, medicinal cannabis was legalised in Australia for palliative care. This was not underpinned by research evidence.

Objectives. To determine whether medicinal cannabis (MC) can lessen symptom burden in patients with advanced cancer receiving palliative care.

Methods. Participants were adults with advanced cancer and a total symptom distress (Edmonton Symptom Assessment Scale (ESAS) score of ≥10/90) who received self-titrated MC oil or matched placebo for 28 days. The primary outcome was ESAS total symptom distress score (TSDS) at day 14. Secondary outcomes were: individual symptom scores, symptom burden over time, patient determined dose, opioid use, depression, anxiety, quality of life and adverse events. In a series of RCTs, placebo has been tested against CBD 100mg/ml (MedCan-1), CBD:THC 10:10mg/ml (MedCan-2) and CBD:THC 20:1mg/ml (MedCan-3).

Results. In MedCan-1, 58 participants on CBD and 63 on placebo reached day 14. The change in TSDS from baseline was -6.2 (SD 14.5) for placebo and -3.0 (SD 15.2) for CBD with no difference between arms (p=0.24). Similarly, there was no difference in proportion of “responders” (reduction in TSDS by ≥6) (placebo 58.7%, CBD 44.8%, p=0.13). All individual symptom scores improved over time in both arms and most participants reported feeling “better” or “much better” at days 14 and 28. There was no effect of CBD on any secondary outcome measure. Adverse events did not differ between arms. In MedCan-2, any contribution of THC to symptom relief is being assessed. MedCan-3 assesses a different cannabinoid combination and secondary outcomes highlighted as being of potential benefit in the previous studies (sleep, anxiety, happiness).

Conclusion. Controlled trials of medicinal cannabis are feasible and popular with patients. As CBD alone does not improve symptom management above that provided by palliative care alone, we continue to investigate the contribution of THC in various cannabinoid preparations.

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POSTER PRESENTATIONS

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The Nematode C. elagans as an Objective Test System to Study Putative Entourage Effects of Cannabis

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Background: The medicinal effects of cannabis varieties on the market cannot be explained solely by the presence of the major cannabinoids Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD). Evidence for putative entourage effects caused by other compounds present in cannabis is hard to obtain due to the subjective nature of patient experience data. C. elegans is a small, transparent organism with a complete nervous system and behavior. Due to its genetic robustness and short life cycle the organism is highly suitable to unravel the effects and mode of action of health related products and compounds.

Objectives: Explore the possibilities of C. elegans as an objective test system to identify compounds involved in the claimed health and entourage effects of cannabis.

Methods: From a medicinal cannabis breeding program a set of both THC rich varieties as well as CBD rich varieties were selected. A consecutive extraction process was applied resulting in a non-polar (cannabinoid-rich) and polar (cannabinoid-poor) extract of each variety. The test model C. elegans was exposed to these extracts in a broad set of bioassays for appetite control, body oscillation, motility, and nervous system function.

Results: Exposing C. elegans especially to the polar and cannabinoid poor extracts resulted in significant effects with respect to appetite control, body oscillation, motility, and nervous system-related functions in a dose-dependent and variety-dependent manner. Interestingly the results obtained by the C. elegans test system showed a high degree of similarity with the effects claimed by human users.

Conclusion: By using C. elegans, we were able to objectively distinguish different effects of different varieties despite the cannabinoid content. C. elegans seems a useful test system for studying entourage effects, for targeted medicinal cannabis breeding programs and product development.

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Delta9-tetrahydrocannabinol conserves cardiovascular functions in a rat model of endotoxemia: involvement of endothelial molecular mechanisms and oxidative-nitrative stress

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Endotoxemia is accompanied by severe cardiovascular dysfunction, in which inflammatory processes and oxidative-nitrative stress play important roles. Recently, several researcher described that inflammatory parameters in endotoxic animal models were altered to a favorable direction as a response to the activation of cannabinoid receptors. Our aim was to examine the effect of cannabinoid treatment on the cardiovascular system in endotoxemia.

Male Wistar rats were treated with LPS (5 mg/kg i.v.) to induce endotoxemia. A group of animals received additional D9-tetrahydrocannabinol THC (10 mg/kg i.p.). 24 hours later we examined their cardiac function by echocardiography. Endothelium-dependent, acetylcholine induced relaxation of the thoracic aorta rings was measured by wire-myography. To evaluate the molecular mechanism, endothelial-NOS, COX-2, cGMP, oxidative stress marker 4-hydroxynonenal (HNE), nitrative stress marker 3-nitrotyrosine (NT), and poly(ADP-ribose)polymer (PAR) was labelled by immunoshistochemistry.

A decrease in the end-systolic and the end-diastolic ventricular volumes with sustained ejection fraction was found in the LPS group, which was not observed in LPS+THC animals. Endothelium-dependent relaxation worsened in the LPS group, however no significant endothelial dysfunction was present in the LPS+THC group compared to controls. cGMP staining density was reduced in both LPS treated groups independent from THC treatment; eNOS labeling was only reduced in the LPS+THC treated animals. COX-2 staining density was only reduced in the LPS+THC treated group. Tissue oxidative (HNE) and nitrative (NT) stress increased after LPS treatment, which was reversed by THC co-treatment. The significant increase in PAR-ylation after LPS was prevented by THC.

Based on our results, we hypothesize that the reduced diastolic filling in the LPS group is a consequence of vascular dysfunction, which was prevented by THC. The mechanism of action of THC is not based on its local effect on aortic NO homeostasis. The reduced oxidative-nitrative stress and detectability of COX-2 suggest the activation of an anti-inflammatory pathway.

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Improving the solubility of cannabinoids as a way to increase their bioavailability

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Introduction: The routes of administration of the *Cannabis ssp.* active ingredients are usually by inhalation while vaping or smoking, or sublingually with the use of oils due to cannabinoids poor solubility, which limits their oral bioavailability. The struggle many scientists face is the improvement of cannabinoids dissolution so that they can be also administered orally.

Aims: The aim of the research was to develop systems for the delivery of cannabinoids present in extracts obtained as a result of the action of supercritical carbon dioxide.

Methods: Cannabinoid delivery systems (CBD, CBDA, CBC) were developed as a result of combining extracts with selected carriers (neusilin US2, and soluplus) obtained by the action of supercritical carbon dioxide (p=6000 psi at 50^{o}C). The antioxidant potential of the systems was determined by using DPPH, ABTS, CUPRAC, and FRAP procedures. Apparent solubility study of cannabinoids form delivery systems was studied in (0.1 M HCl, phosphate buffer pH 6.8, FaSSIF/FeSSIF), while their GIT permeability was studied using a parallel artificial membrane permeability assay (PAMPA).

Results: As a result of the development of cannabinoid delivery systems, an improvement in their dissolution rate and an increase in penetration through membranes simulating the walls of the gastrointestinal system was obtained. In view of the confirmed antioxidant properties and the possibility of inhibiting enzymes showing significant activity in the development of neurodegenerative diseases for the extracts obtained as a result of the action of supercritical carbon dioxide, the improvement of cannabinoid dissolution makes these delivery systems very prospective.

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Cannabis-Based Medicinal Products in the Management of Emotionally Unstable Personality Disorder (EUPD): A Narrative Review and Case Series.

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Background: Emotionally unstable personality disorder (EUPD) is a common mental health disorder, manifesting with a range of chronic and debilitating symptoms including impaired social functioning, unstable mood, and risky impulsive or self-injurious behavior. Recent studies suggest that impaired functioning of the endocannabinoid system in key brain regions responsible for emotional processing and stress response may underlie the manifestation of EUPD symptoms. Current NICE guidelines do not provide any recommendations for pharmacological treatment of EUPD which poses a significant challenge for the clinical management of these patients.

Objective: To evaluate the potential of cannabis-based medicinal products (CBMP) as a treatment option in patients suffering from EUPD.

Methods: Here we present a case series of 7 participants diagnosed with EUPD that received treated with cannabis-based medicinal products (CBMPs). Participants were given an initial consultation and followed up one month after CBMPs prescription. Clinical improvement in symptoms was assessed by completion of the Clinical Global Impression Improvement scale (CGI-I), as well as the Patients' Global Impression of Change scale (PGIC).

Results: Most participants were under the age of 30 and presented psychiatric comorbidities. Six participants reported feeling "better, and a definite improvement that has made a real and worthwhile difference" and one participant did not report any improvement. Scoring from the CGI-I and PGIC were correlated, with the patient and the prescribing psychiatrist agreeing on the overall degree of improvement. None of the participants reported adverse side effects associated with CBMPs.

Conclusion: Our results indicate that treatment with CBMPs was effective, as 6 participants reported a noticeable improvement in their symptoms and functioning, and well tolerated. Although promising, further research is needed to ascertain the long-term tolerability, efficacy, and dosing strategy for CBMPs in EUPD.

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Effects of Oral Cannabinoids on Systemic Inflammation and Viral Reservoirs in People with HIV on Antiretroviral Therapy: Results of the CTNPT 028 Clinical Trial

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Background: Despite successful antiretroviral therapy (ART), chronic HIV infection is characterized by persistent inflammation which drives development and progression of comorbidities.
Objective: To determine whether oral cannabinoid capsules can reduce systemic inflammation in people living with HIV (PWH).
Methods: Ten PWH (median age: 57.5 years, 8 males) on ART were randomized (n=5/group) to increasing doses of oral Δ9-tetrahydrocannabinol(THC): cannabidiol(CBD) combination (THC/CBD: 2.5/2.5 to 15/15mg daily) capsules or CBD-only (200 to 800mg daily) capsules, for 12 weeks. Blood was prospectively analyzed as part of the clinical trial before starting and after completing cannabinoid treatment. Hematology and biochemistry profiles were measured to assess the safety. Plasma levels of inflammatory markers interferon (IFN)-g, tumor necrosis factor (TNF)-a, interleukin (IL)-1b, IL-6, IL-8, and IFN-γ-induced protein (IP)-10, and anti-inflammatory IL-10 were determined using a Luminex assay, and Lipopolysaccharide (LPS), sCD14, sCD27, gut damage markers regenerating family member (REG)-3α and intestinal fatty-acid binding protein (I-FABP) were quantified by ELISA. Total HIV DNA and cell-associated RNA were measured in blood CD4+ T-cells and in cell pellets from semen by ultra-sensitive qPCR, and cell-free viral RNA was measured in blood and semen supernatant. Non-parametric Wilcoxon rank test was used for statistical analyses.
Results: Eight individuals completed the study. Cannabinoids did not alter participants' hematology/biochemistry profiles. CD4 count and CD4/CD8 ratio were stable and viral load remained suppressed throughout the study. Cannabinoids significantly reduced mean plasma levels of the following inflammatory markers from initiation versus the end of the intervention: IFN-g (10.98-8.54 pg/ml; P=0.03), TNF-a (2.61-2.12 pg/ml; P=0.02), IL-1b (0.62-0.39 pg/ml; P=0.02), and REG-3α (5621-4950 pg/ml; P=0.04). Cannabinoids had no significant effect on HIV DNA and RNA levels in blood or semen, nor other plasma inflammatory markers.
Conclusions: Cannabinoids reduced some inflammatory markers and gut microbial translocation markers of in PWH, providing rationale for a larger clinical trial.

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The C4EB study - Transvamix® (10% THC / 5% CBD) to treat chronic pain in Epidermolysis Bullosa: A protocol for an explorative randomized, placebo controlled, and double blind intervention crossover study

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Patients with the genetic blistering skin condition epidermolysis bullosa (EB) report severe pain as a consequence of skin and mucous membrane lesions including blisters, wounds, and scars. Adequate symptom alleviation is not often achieved using conventional pharmacologic interventions. Finding novel approaches to pain care in EB is imperative to improve the quality of life of patients living with EB. There are several anecdotal reports on the use of cannabinoid-based medicines (CBMs) by EB patients to reduce the burden of symptoms. However, controlled clinical investigations assessing these reported effects are lacking.

As the pain quality “unpleasantness” delineates EB pain, we hypothesize the modulation of affective pain processing in the brain by way of intervention with CBMs comprising the cannabinoids Δ-9-tetrahydrocannabinol and cannabidiol - objectified by functional magnetic resonance imaging (fMRI).

The C4EB study is an investigator-initiated, single-centre, randomized, double-blind, placebo-controlled and crossover trial. Adult patients with the diagnosis epidermolysis bullosa, reporting chronic pain will be eligible to participate. Following baseline measurements, participants will be randomized to receive the sublingually administered interventions placebo and Transvamix® in forward or reversed orders, each for two weeks and separated by a washout. The primary outcome is the difference in numeric rating scale pain scores between grouped interventions, using affective descriptors within the Short-form McGill Pain Questionnaire-2. Secondary outcomes include pain self-efficacy, concomitant analgesic medication-use and adverse events. Additionally, fMRI will be employed to assess brain connectivity related to neuroanatomic pain circuits at baseline, placebo and Transvamix® interventions.

The study was approved by the ethical committee at the University Medical Center of Groningen in the Netherlands. Results will be submitted for publication in a peer-reviewed journal.

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Clinical research evidence supporting administration and dosing recommendations of medicinal cannabis as analgesic in cancer patients

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The analgesic potential of Cannabis sativa L. - based medicinal cannabis products for treatment of cancer associated chronic pains has gained increased interest in recent years. To ensure a controlled distribution of these products and investigate their therapeutic potential, several countries have established so-called pilot trials. Many doctors, however, are hesitant to prescribe medicinal cannabis primarily due to lack of research evidence regarding the products´ efficacy, safety and thus questionable dosing guidelines. This review aims to elucidate clinical research supporting administration of medicinal cannabis in cancer patients for analgesic purposes. The cannabinoids´ effects on the endocannabinoid system (ECS) and its implication in pain regulation is included to illustrate the complexity related to this research field. Published clinical studies on medicinal cannabis primarily consist of observational studies and only one pilot randomized controlled trial (RCT), where more RCTs exist on the cannabis-based product, Sativex®. The studies indicate analgesic potential, however non-significantly, for most patients and with acceptable safety profile. Summarizing, high-quality RCTs are scarce in this research field, and the limitations of the observational studies complicates interpretation of clinical outcomes. Despite discrepancy among the studies, they do show indications for administration and dosing regimens providing analgesic effects for some cancer patients.

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Patient Experiences, Attitudes, and Beliefs Towards the Use of Medicinal Cannabis: A Scoping Review

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Background: Recent years have seen a resurgence in political and public health related interest for the legalisation of cannabis for medical purposes. Research is needed that offers a nuanced summary of the evidence regarding the experience and viewpoint of patients who undergo this form of treatment. A scoping review was thus undertaken to explore the multifaceted nature of this topic and the corresponding range of available research evidence.

Objective: To synthesise knowledge from the existing research literature about patients' experiences, attitudes and beliefs towards the use of medical cannabis and cannabis-based medicines.

Methods: A systematic search for peer-reviewed original research articles and reviews was performed in EMBASE, Scopus, PubMed and the Cochrane Library. Characteristics of included studies were organised into a predesigned data charting form, and thematic analysis was used to identify key themes in the findings.

Results (preliminary): The search yielded 6504 records, 72 of which met inclusion criteria. Key themes and subthemes highlighted the therapeutic importance and predominant tolerability of medical cannabis and cannabis-based medicines for a variety of disease-related symptoms. Patients experienced barriers in accessing treatment due to the regulatory logistics of healthcare systems and perceived stigmatisation on behalf of healthcare professionals. Furthermore, patients expressed their personal beliefs about the healing power of cannabis and its perceived superiority compared to conventional medicines.

Conclusions (preliminary): This review highlights a disparity between generally positive, patient-relayed experiences concerning the therapeutic and opioid sparing effect of medical cannabis and cannabis-based medicines, despite some experiencing severe adverse effects, and the consensus in the academic community that definitive research on these effects is lacking. More high-quality clinical trials and observational studies are needed to investigate the beneficial, harmful, and opioid-sparing effect of the medicines, as well as patient experiences, attitudes and beliefs that may contribute to a more nuanced evidence-base.

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Inhaled Δ9-Tetrahydrocannabinol (THC) is Without Effect on Respiration and Does Not Enhance Oxycodone-Induced Respiratory Depression: A Randomized Controlled Trial in Healthy Volunteers

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Background: In humans, the effect of cannabis on ventilatory control is poorly studied and consequently the effect of Δ9-tetrahydrocannabinol (THC) remains unknown, particularly when THC is combined with an opioid.

Objectives: We studied the effect of THC on breathing without and with oxycodone pretreatment. We expected that THC causes respiratory depression, which is amplified when THC and oxycodone are combined.

Methods: In this randomized controlled trial, healthy volunteers were treated with 100 mg inhaled Bedrocan®, a pharmaceutical-grade high-THC cannabis variant, that contains 21.8% THC and 0.1% cannabidiol, following placebo or 20 mg oral oxycodone pretreatment; THC was inhaled 1.5 and 4.5-h after placebo or oxycodone intake. The main endpoint was isohypercapnic ventilation at an end-tidal PCO2 of 55 mmHg ($\dot{V}E55$). $\dot{V}E55$ was measured at 1-h intervals for 7 hours following placebo/oxycodone intake.

Results: In 18 volunteers of either sex, oxycodone produced a 30% decrease in $\dot{V}E55$, while placebo was without effect on $\dot{V}E55$. The first cannabis inhalation changed $\dot{V}E55$ from 20.3 (3.1) to 23.8 (2.4) L min-1 ($p = 0.06$) after placebo and from 11.8 (2.8) to 13.0 (3.9) L min-1 ($p = 0.83$) after oxycodone pretreatment. The second cannabis inhalation had similarly no effect on $\dot{V}E55$ (placebo/THC $p = 0.94$; oxycodone/THC $p = 0.99$).

Conclusion: In humans, THC has no effect on ventilatory control following placebo or oxycodone pretreatment. This suggests that CB receptors do not act at human respiratory neuronal pathways in the brainstem, or that cannabinoid type 1 receptor-induced respiratory depression is offset by an opposing effect at cannabinoid type 2 receptors.

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Safety Assessment in Rats after Chronic Exposure to Cannabidiol and Cannabigerol

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Background

Cannabidiol (CBD) and cannabigerol (CBG) are the two main nonpsychotropic phytocannabinoids with high application potential in drug development. Both substances are redox-active and are intensively investigated for their cytoprotective and antioxidant action in vitro.

Objectives

In this study, we focused on an in vivo safety evaluation and the effect of CBD and CBG on redox status in rats in a 90-d experiment.

Methods

The substances were administered orogastrically at a dose of 0.66 mg synthetic CBD or 0.66 mg/1.33 mg CBG/kg/day.

Results

CBD produced no changes in red or white blood count or biochemical parameters in the blood in comparison to the control (no cannabinoid administration). No deviations in the morphology or histology of the gastrointestinal tract and liver were observed. After 90 d of CBD exposure, a significant improvement in redox status was observed in the blood plasma and liver. The concentration of malondialdehyde and carbonylated proteins was reduced compared to the control. In contrast to CBD, total oxidative stress was significantly increased, which was accompanied by an increased level of malondialdehyde and amounts of carbonylated proteins in CBG-treated animals. Hepatotoxic (regressive changes) manifestations, disruption of white cell count, and alterations in the ALT activity, level of creatinine and ionized calcium were also found in CBG-treated animals.

Conclusion

Both CBD and CBG structures include a resorcinol moiety. In CBG, there is an extra dimethyloctadienyl structural pattern, which is most likely responsible for the disruption to redox status and the hepatic environment. The presented results could be used in further investigations of the effects of CBD on redox status and also could contribute towards opening up critical discussion about the applicability of other nonpsychotropic cannabinoids.