Oral CBD-rich cannabis induces clinical but not endoscopic response in patients with Crohn's disease, a randomized controlled trial

Timna Naftali[1,2],Lihi Bar-Lev Schleider[3],ShlomoAlmog[2], David Meiri[4],Fred M. Konikoff[1,2]

[1]Institute of Gastroenterology and Hepatology, Meir Medical Center,KfarSaba,Israel

[2]Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

[3]Research Department, Tikun-OlamCannbit Pharmaceuticals, Tel Aviv, Israel

[4]Department of Biology, Technion-Israel Institute of Technology, Haifa, Israel

Short title: Oral CBD-rich cannabis for Crohn's disease

Address for correspondence

Dr Timna Naftali

Department of Gastroenterology and Hepatology, Meir Hospital, 59 Tchernichovsky St, Kfar Saba, Israel

Telephone: 97297472580Fax:97299492725

E-mail:timna.naftali@clalit.org.il

Abbreviations

THC, Δ9-tetra-hydrocannabinol

CBD, cannabidiol

ECS, endocannabinoid system

CD, Crohn's disease

CDAI, Crohn's disease activity index

CRP, C-reactive protein

SES-CD, simple endoscopic score for Crohn's disease

IBD, Inflammatory bowel disease

IQR, interquartile range

QOL, Quality of life

SD, Standard Deviation

Abstract

Aims: Despite reports that medical cannabis improves symptoms in Crohn's disease (CD), controlled studies evaluating disease response are lacking. This study assessed the effect of cannabidiol (CBD)-rich cannabis oil for induction of remission in CD.

Methods: In a double-blind, randomized, placebo-controlled single center trial, patients received orally eithercannabis oil containing160/40mg/ml cannabidiol/ tetrahydrocannabinol (CBD/THC) or placebo for eight weeks. Disease parameters including CD activity index (CDAI), and simple endoscopic score for CD (SES-CD) were assessed before and after treatment. In a subgroup of patients, blood samples were collected for CBD and THC plasma levels.

Results: The study included 56 patients**,** age 34.5±11 years, men/women 30/26 (54/46%), 30in cannabis and 26 in placebo groups. CDAI at recruitment and after eight weeks was282(IQR243-342) and 166 (IQR 82-226) and 264(IQR 234-320) and 237(IQR 121-271) ($p<0.05$) in the cannabis and placebo groups, respectively. Median QOL score improved from 74 for both groups at baseline to 91 (IQR 85-102) and 75 (IQR 69-88) after 8 weeks in the cannabis and placebo groups, respectively ($p=0.004$). SES-CD was 10 (7-14) and 11 (IQR7-14), and 7 (4-14) and 8 (IQR 4-12;$p=0.75$)before and after treatment, in the cannabis and placebo groups, respectively. Inflammatory markers (CRP, calprotectin) remained unchanged.

Conclusions: Eight weeks of CBD-rich cannabis treatment induced significant clinical and QOL improvement without significant changes in inflammatory parameters or endoscopic scores. **The oral** CBD-rich cannabis extract was well absorbed. Until further studies are available, cannabis treatment in Crohn's disease should be used only in the context of clinical trials.

ClinicalTrials.gov:NCT01826188

Key words: Crohn’s disease, cannabis, cannabidiol

Introduction

Despite the extensive progress made in the treatment of Crohns disease (CD) in the last decade, response is still only 40-60%, and there is no cure. Therefore, it is not surprising that patients with CD turn to alternative treatments, including medical cannabis(1). About 15% of CD patients report using cannabis to alleviate their symptoms, but evidence about the efficacy of this treatment is lacking(2). Most studies regarding the use of cannabis in IBD are limited to retrospective observational studies, with data about the prevalence of cannabis use among IBD patients but not about the dose, mode of consumption or change in disease activity(3,4). The predominant and best known cannabinoids are Δ9-tetra-hydrocannabinol (THC), and cannabidiol(CBD), but the cannabis plant contains about 100 different cannabinoids, as well as other compounds such as terpenes and flavonoids(5,6) It is reasonable to assume that different strains and compositions of cannabis will have different effects(7,8); however, most studies do not analyze the exact composition of the cannabis they investigate. We previously performed a double-blind, placebo-controlled study of THC-rich cannabis for induction of remission in CD, showing that cannabis may be of clinical benefit(9).

Recreational cannabis is usually THC-rich and primarily consumed by smoking. Likewise, most available clinical data have been derived from patients using cannabis via smoking. Moreover, our previous placebo-controlled study also used cannabis provided in cigarettes (14); not a preferred mode of administration of medical therapy. Hence, information about healthier routes of administration is needed.

The aim of this study was to evaluate efficacy of oral use of cannabis oil rich in CBD for induction of clinical, laboratory and endoscopic remission in mild-to-moderate Crohn’s disease.

Materials and methods

Study design

We conducted a single-center, prospective, randomized, double-blind, placebo-controlled, parallel-arm, clinical study. The study took place in the IBD clinic of the institute of gastroenterology, Meir Hospital, Kfar Saba, Israel from 2013 to 2018. The protocol included a two-week *screening period* to evaluate for baseline symptoms, an eight-week *treatment period* and a two-week *follow-upperiod* after the treatment was discontinued.

Patients were evaluated by medical interview, physical examination, blood and stool tests at baseline (end of screening; week 0), after two weeks of study intervention (week 2), end of intervention (week 8), and end of follow-up period (week 10). Colonoscopy was performed at screening (week 0) and after eight weeks of treatment. Primary outcome was defined as a statistically significant reduction in CDAI and improvement in QOL. Secondary outcomes were remission of disease ,i.e., CDAI of less the 150 points, improvement of at least one point in Endoscopic disease activity index, improvement of CRP and calprotectine and improvement of at least 30 points in quality of life as measured by the SF 36.

Blinding and randomization

Patients were randomly assigned using a block method in blocks of 5 in a 1:1 ratio to receive either high CBD cannabis oil or placebo(10). The study compound was prepared and randomized in the TikunOlam laboratory, outside the hospital. Laboratory personnel had no access to the study participants. The code was kept outside the hospital and the physicians conducting the study had no access to it.

Identical-appearing placebo was made of olive oil containing chlorophyll. Patients and investigators were blind to the treatment through the duration of the study.

Study population

The study population included male and female patients ages 20 to 80 years, with mild to moderate CD diagnosed at least three months prior to enrollment. Disease activity was determined by Crohn's disease activity index (CDAI) ≥200 and simple endoscopic score for Crohn's disease (SES-CD)- >2.

Patients continued their previous CD medications if they were on a stable dose; specifically, at least four weeks for 5-ASA or three months for immunomodulators and biologic treatments. Steroids were permitted at a maximal dose of 20mg prednisone and if the patients were on a stable dose for at least eight weeks prior to enrollment. Patients were not allowed to change their medications during the study. Exclusion criteria included use of cannabis, whether medical or recreational, pregnancy or lactation, severe CD (CDAI >400), ulcerative colitis, known psychiatric disorder or addiction traits based on self-reporting or noted in the patient's electronic medical record. Patients scheduled for surgery within the study period were excluded.

Study compound and dosing

Treatment was provided orally in the form of oil, which was extracted from *Cannabis* Indica "Avidekel" (courtesy of Tikun-Olam Ltd., Tel Aviv, Israel). Tikun-Olam has ISO9001 and Hazard Analysis Critical Control Point (HACCP) certifications issued by the Standards Institute of Israel.

The Avidekel oil contained 16% CBD and 4% THC. Each oil drop is approximately 0.05 ml containing about 8 mg CBD and 2 mg THC. For the full details of the

composition see Figure 1. Patients in the control group received placebo oil containing olive oil and Chlorophyll so it will look and smell similar.

The oil used in the study was analyzed for cannabinoid content in the Laboratory of Cannabinoid Research, the Technion, Haifa, Israel. Reagents, analytical standards, and general methodologies for phytocannabinoid extraction and analysis from cannabis were conducted according to previously published methods, and are fully described in the supplement (5,11)(12). .

Since cannabis products differ in their composition, we will refer to the study compound used in the study not as "cannabis" but as the "studyproduct".

Patients were instructed to install the oil under the tongue and roll it in their mouth until absorbed. We chose this oral route of administration in order to avoid exposure to noxious pyrolytic by-products formed by combustion associated with smoking.

The starting dose was 1 drop twice daily before meals(8 mg CBD and 2 mg THC per drop), gradually increased until the patient felt a satisfactory effect (i.e., reduction in abdominal pain and diarrhea) or until side-effects occurred. The maximal allowed dose was 20 drops per administration, (i.e., 40 drops/day containing a total of 320 mg CBD and 80 mg THC/day). This gradual dosage increase was chosen to decrease potential side-effects, as previously reported(13).

Pharmacokinetic study

A subgroup of 7 patients participated in the pharmacokinetic study. Blood samples for THC and CBD levels were drawn before, and 10, 20, 60, 120, 180, and 240 minutes after cannabis consumption. The plasma samples were stored frozen at -80°C until analysis. The cannabinoid analysis was performed at NMS Labs (Willow Grove, PA, USA), an accredited laboratory by ANAB-ASCLD/LAB ISO 17025, using validated

high-performance liquid chromatography/tandem mass spectrometry. The reporting limits of THC and CBD are 0.5 and 0.1 ng/ml plasma, respectively.

Delay between cannabis extract administration and the beginning of absorption (T_{lag}), maximum THC plasma concentration (C_{max}) and time to reach C_{max} (T_{max}) were derived directly from the experimental data. Half-life time of absorption ($T_{½,abs}$)was calculated as lan2/λ_{abs}, where $\lambda_{abs}$is the initial slop on the semi Lan scale. Area under the plasma THC concentration-time curve (AUC) was determined by linear trapezoidal non-compartmental analysis (Win-Nonlin Pro version 2.0; Pharsight, Mountain View, CA, USA). The AUC was extrapolated to infinity ($AUC_{0\rightarrow infinity}$) by the addition of C_{last}/λ_Z, where C_{last} and λ_Z are the last measured THC concentration and the terminal slope on the semi-Lan scale, respectively.

Assessment of clinical effect

Patients were evaluated by medical interview, physical examination, blood and stool tests, and endoscopy. Information collected from patients' records included demographic data, smoking history, past medical history (including history of drug abuse and psychiatric co-morbidity, if any), CD history, past and present medications, family history of IBD, and results of recent blood tests, endoscopic and imaging studies.

For clinical assessment we used the CDAI, as well as additional sub-analyses on specific variables of interest, including number of bowel movements per day, abdominal pain and general well-being.

Quality of life (QOL) was assessed at baseline (week 0) and at the end of intervention (week 8) using the Short Form-36 survey (14). The higher the score, the better is the QOL.

Patients were also asked to report their general satisfaction with the treatment on a 7-point Likert scale (1=not at all satisfied to 7=very satisfied) and overall improvement of specific symptoms including general health, appetite, libido and concentration on a 5-point Likert scale (1=significant improvement to 5= worsening).

Assessment of effect on inflammation

Inflammatory activity was assessed with laboratory blood tests, stool calprotectin and endoscopic parameters. Blood tests included complete blood count, liver and kidney function, and C-reactive protein (CRP). Colonoscopies were performed at baseline (week 0) and end of intervention (week 8) by physicians who were blinded to the patient's study group. Endoscopic disease activity was assessed using the SES-CD(15,16).

Assessment of side effects

Adverse effects, including symptoms of drug addiction as defined by the DSM-IV(17), were recorded at weeks 2 and 8 and rated for severity on a 0 to 7 scale. During study visits, patients were asked to complete a questionnaire including general questions about the perceived effect, if any, of cannabis on their health, and how long it took for the effect to occur. They were also asked to mark changes in sleep, pain, abdominal swelling, appetite, general well-being and general satisfaction with the treatment on a 1-7 Likert scale, where 1 =great improvement, 7 = severe deterioration. Additionally, patients were asked whether they experienced any negative side-effects

including specific questions on visual distortion, restlessness, behavioral change, confusion, decreased memory, dizziness, cough and shortness of breath.

Statistical analysis

Categorical variables were reported as number and percentage. Continuous variables were evaluated for normal distribution using histogram and QQ plot. Baseline characteristics at first visit and third visit evaluation were compared between groups using independent sample t-test or Mann-Whitney test for continuous and ordinal variables, and Chi-square test or Fisher exact test were used for categorical variables. In each group, differences between the first and third visits were tested using paired sample t-test or Wilcoxon test for continuous and ordinal variables. Generalized estimating equation models were used to observe changes between the groups during the follow-up period while controlling for age, gender and disease duration. This was evaluated using interaction between time and group. Corrections for multiple comparisons were done using the False Discovery Rate method.

Assuming a minimum difference of 100 points in the CDAI score between the treatment group and the placebo group, with a standard deviation of 111 (based on our previous study(9)) with an alpha of 0.05 and a power of 80%, the calculated sample size was 21 patients in each group.

All statistical tests were 2-sided and $p<0.05$ was considered statistically significant. SPSS software was used for statistical analysis (SPSS statistics for windows, ver. 25, IBM Corp, Armonk, NY, USA).

Ethical considerations

The study was approved by the Ministry of Health Cannabis Authority Ethics Committee and the Meir Medical Center Ethics Committee (study number 0196-12-

MMC). All participants provided written informed consent before any study-related procedure was carried out. All procedures were carried out in accordance with relevant guidelines and regulations. The study was registered at ClinicalTrials.gov: NCT01826188.

Results

Study population

Altogether, 111 patients were screened, of these, 55 were excluded: 20 did not consent, mainly for fear of receiving placebo,18 had inactive disease with CDAI<200, 13 were in endoscopic remission at colonoscopy (including terminal ileum). Other reasons for non-recruitment were (one patient each) breast feeding, history of mental illness, age under 20, and active military service. Eventually, 56 patients with CD were recruited and completed the study; 30 in the study extract group and 26 in the placebo group. Demographic details are listed in Table 1.Details of past and present CD treatment are listed in Table 2.

Dosing and pharmacokinetics

Patients started with a dose of 2 drops a day, equivalent to 16 mg CBD and 4mg THC, and increased it gradually. The final volume taken per administration in the study group was 10 drops (interquartile range (IQR) 5-14), equivalent to 0.5 ml (IQR 0.25-0.7) and in the placebo group 15 drops (IQR10-31), equivalent to 0.75 ml(IQR 0.5-1.5), p=0.004. This corresponds to a final median dose taken by the study group of 80mgCBD (IQR 52-108) and 20mgTHC (IQR 13-27).

Seven patients were included in the pharmacokinetics study. Following oral administration of the study extract, for CBD, mean T_{lag} was 55±54 minutes, mean C_{max} was 8.1±5.4 ng/ml, mean T_{max} was 102±16 minutes, $T_{½,abs}$ was 39±25 minutes and $AUC_{0\rightarrow infinity}$ was 2,419±1,539 (ng/ml)*min. For THC, mean T_{lag}±SD was 63±63 minutes, mean C_{max} was 3.0±2.1, mean T_{max} was 108±45 minutes, $T_{½,abs}$ was 33±16 minutes and $AUC_{0\rightarrow infinity}$ was 643±134 ng/ml*min., as depicted in Figure 1.

Clinical effect

After 8 weeks of treatment, median CDAI was 166 (IQR 82-226) in the cannabis extract group and 237 (IQR 121-271) in the placebo group (p=0.038), so the primary endpoint was met. However, this change, can be attributed mostly to improvement of general well-being and abdominal pain, as the change in number of bowel movements was not significant. Similarly, QOL was significantly improved in the study group but not in the placebo group, with a median of 91 (IQR 85-102) vs.75 (IQR 69-88), p=0.004. The secondary outcome of improvement of at least 30 points in quality of life was not met (Table 3).

In the within-group analysis, there was significant improvement within the extract group in CDAI, number of bowel movements, abdominal pain and quality of life, whereas the placebo group showed an improvement only in the CDAI and number of bowel movements (Table 4).

In multivariate analysis, after controlling for age, gender and illness duration, there was no significant difference between the groups regarding CDAI (p=0.072), number of bowel movements (p=0.77), abdominal pain (0.078), SES–CD (p=0.185), quality of life (p=0.143), calprotectin (p=0.13) or CRP (p=0.54).

Effect on inflammation

No significant change was observed in any of the laboratory parameters, including CRP and calprotectin, so this secondary endpoint was not met (Tables 3 and 4). Elevated CRP was observed in 21 patients of the study group and 18 of the placebo group at the beginning of the study. At the end, elevated CRP was observed in 21 and 18 patients (not necessarily the same patients) in the study and control groups, respectively. Regarding calprotectin, when taking a cutoff of 100μg/g, in the study group 11 patients had elevated calprotectin at the beginning, and 10 at the end, the corresponding numbers in the placebo group were 12 and 11.

Normalization after 8 weeks of initially high CRP was observed in five patients of the study group but only in one in the placebo group. In two patients in the placebo group CRP was normal at the beginning of the study but was elevated after 8 weeks of treatment. In three patients in the study group and four in the placebo group calprotectin was high before study initiation and normalized at the end of the study.

SES-CD score at week 8 was lower in the extract group compared with the placebo group, but the difference did not reach statistical significance. The within-group analysis, however, showed a significant reduction of the SES-CD score in the placebo but not in the extract group, the secondary endpoint of improvement of at least one point in Endoscopic disease activity index was not met (Table 3).

Well-being and adverse effects

When asked whether they felt that the treatment improved their health, the answer was positive in 16/20 in the cannabis group and 8/20 in the placebo group (p=0.01). When asked how long it took to feel an effect from the treatment, 75% of the extract group said the change was immediate, whereas 75% of the placebo group said they

felt the change within two weeks (p=0.012). Patients in the extract group reported significant improvements in sleep, pain, abdominal swelling, appetite, general well-being and general satisfaction with the treatment (see supplementary Table 1).

Patients were also specifically asked whether they experienced any adverse effects, such as visual distortion, restlessness, behavioral change, confusion, decreased memory, dizziness, cough or shortness of breath. The only symptom that was more common in the extract group was decreased memory, a symptom that we also observed in our previous study(18), but that was not statistically significant.

After the 8 week treatment period, none of the patients receiving cannabis reported difficulty to stop the use (Table 5).

Discussion

This is the first double-blind placebo-controlled study to investigate the effects of oral cannabis oil on both clinical and endoscopic outcome in Crohn's disease. Furthermore, the composition and dosage of cannabis given to the patients was precisely analyzed, and blood levels were checked. Our study met the pre-determined end points in terms of clinical and QOL improvement, but did not meet the endpoint of improvement in endoscopic findings and inflammatory markers. The findings show that 8 weeks of treatment with CBD-rich cannabis oil extract can reduce CDAI to a mildly active disease level and improve quality of life., Within group analysis comparing visit 1 to visit 3 showed a significant improvement in the study group of CDAI, number of bowel movements, abdominal pain and quality of life (Table 3). Improvement in CDAI and number of bowel movements was also noted in the placebo group, but to a lesser degree. When normalized for age, gender and illness duration, the between group differences were no longer significant. This may be due

316 to the relatively small number of study participants and to a strong placebo effect. It is
317 worth noting that symptomatic improvement in the study group was immediate,
318 whereas if it occurred in the placebo group it was felt only after 2 weeks. Moreover,
319 the placebo group consumed a larger volume of the study compound, presumably
320 because they did not experience any beneficial or side-effects.

321 Improvement in sleep, pain, abdominal swelling, appetite and general well-being, all
322 important parameters contributing to QOL, was significantly more pronounced in the
323 extract treated group.

324 The potential benefits of cannabis for treating different diseases have been of great
325 interest. While CD is considered an acceptable indication for the use of medical
326 cannabis, the evidence supporting its benefits is very limited. Unfortunately, most
327 studies regarding cannabis use in IBD are descriptive or limited to reports on
328 prevalence of use (19),(2,3) with very limited, or uncontrolled data about the dose and
329 mode of cannabis consumption, as well as efficacy. It is particularly challenging to
330 perform cannabis studies because of the difficulty in creating a placebo, the huge
331 variety of cannabis plants, as well as the status of cannabis as an illicit drug(20). In
332 this study, we tried to overcome these obstacles by using well-controlled cannabis
333 content. We used the specific Avidekel strain with a known composition that is rich in
334 CBD, contains less THC, and has a known composition of terpenes. In addition, the
335 cannabis was consumed orally rather than by smoking; thus, avoiding exposure to
336 noxious pyrolytic by-products produced by smoking. This form of cannabis
337 composition and consumption results in reduced psychotropic effects, longer
338 absorption time and increases the local direct interaction of the cannabinoids with the
339 target site. The limited availability of applicable pharmacokinetic and
340 pharmacodynamic information highlights the need to initiate prescribing cannabis

medicines using a “start low, go slow and stay low” approach, carefully observing the patient for desired and adverse effects(16) an approach that was also used in other studies (21).

Patients in the active arm experienced improvement in symptoms; without improvements in markers of inflammation and endoscopic findings. This is in contrast to many animal studies of IBD, which showed decreased inflammation(22), and to some previous humane studies(23,24). The lack of improvement in inflammation could be due to the relatively short duration of the study. It is also possible that the specific derivative used in our study was less effective and an improved composition or higher CBD dose would achieve better results. However, improvement in QOL is an important therapeutic goal, and in the appropriate circumstances, addition of cannabis could help patients cope with the burden of disease.

Various studies have shown that CBD has an anti-inflammatory effect, whereas THC has analgesic and psychotropic effects(25). The combination of THC and CBD is synergistic, enhancing the analgesic and relaxation effects and attenuating the psychotropic effects(26). Our findings suggest that a daily dose of CBD/THC improved pain, mood, sleep, appetite, satisfaction, and general well-being, while adverse effects were minimal, mild in severity and reversible. None of the participants withdrew because of tolerability issues. As the toxicity of CBD is very low, it is possible that raising the ratio of CBD:THC further could improve the anti-inflammatory effect and even attenuate the psychotropic effects.

Other components present in the cannabis plant, such as terpenes, may also have a synergistic therapeutic effect(27), but previous studies on cannabis use did not report a detailed composition. The data reported in our study should be explored further in

future studies, to identify the more effective terpenes that contribute to the effect of cannabis.

In the present study in CD patients, we observed plasma concentration-time profiles of CBD and THC similar to those previously reported (27,28). As depicted in Figure 1, the oral delivery of CBD and THC is characterized by a latency period of an hour post-delivery, slow absorption and low CBD and THC peak plasma concentrations occurring within about 2 hours (29,30).In several studies, $C_{max}$was observed as late as 4 and even 6 hours(31,32). It is worthwhile noting the high inter-individual variations in the pharmacokinetic parameters following oral intake of CBD and THC. This could be due to multiple factors such as erratic absorption, poor oral bioavailability (estimated to be as low as 6%(33)), fast distribution to fat tissues followed by slow redistribution back into the blood stream, significant first-pass metabolism and genetic polymorphism of the metabolic enzymes.

The strength of our study lies in the accurate dosage of cannabis with a known composition and with the monitoring of blood levels, as well as clinical, laboratory and endoscopic responses. The drawbacks are the relatively short treatment period and the small groups. Our results are obviously applicable to the specific cannabis derivative that we used and not necessarily for others. Future studies should be larger and longer.

In summary, in this double-blind, placebo-controlled study, we have shown that an orally administered CBD-rich cannabis extract can induce symptomatic improvement in patients with mild-to-moderate CD without significant changes in inflammatory markers or endoscopic scores. Hence, while our data may provide some promise for CD patients, currently, cannabis should be reserved for clinical trials and research

purposes. Future studies are warranted to explore cannabis combinations, dosages and modes of use that might be effective in human IBD.

Authorship

Authors Contributions

T. N.	Study design, Patient recruitment, data collection and data analysis and writing the first draft of the paper
L. B.S.	Study design, preparation of study compound, critical revision of the article
S.A.	Pharmacokinetic analysis, literature search analysis and interpretation of data, figures, critical revision of the article
D. M.	Analysis of the study compound, analysis and interpretation of data, figures, critical revision of the article
F. M. K.	Study design, patient recruitment, critical revision of the article

All authors have approved the final draft submitted.

Funding: the cannabis used in the study was supplied by Tikun-Olam, Israel.

Potential competing interests*:* Author Lihi Bar Lev Schleider is an employee of Tikun-OlamCannbit Pharmaceuticals, a cannabis manufacturing company, the cannabis used in the study was supplied by Tikun-Olam. All other authors have no conflicts to declare.

F.M.K. was supported, in part, by the Josefina Maus and Gabriela Cesarman Chair for Research in Liver Diseases, Sackler Faculty of Medicine, Tel Aviv University.

Data Availability Statement: The data underlying this article will be shared on reasonable request to the corresponding author.

References:

1. **Storr M, Devlin S, Kaplan GG, Panaccione R, Andrews CN. Cannabis use provides symptom relief in patients with inflammatory bowel disease but is associated with worse disease prognosis in patients with Crohn's disease. Inflamm Bowel Dis. 2014 Mar;20(3):472–80.**

2. **Lal S, Prasad N, Ryan M, Tangri S, Silverberg MS, Gordon A, et al. Cannabis use amongst patients with inflammatory bowel disease. Eur J Gastroenterol Hepatol. 2011 Oct;23(10):891–6.**

3. **Weiss A, Friedenberg F. Patterns of cannabis use in patients with Inflammatory Bowel Disease: A population based analysis. Drug Alcohol Depend. 2015 Nov 1;156:84–9.**

4. **Pi S, Rosenfeld G, Enns R, Bressler B, Wong A, Enns C, et al. Patterns and motivations of *Cannabis* use amongst patients with inflammatory bowel disease. GastroHep - The International Journal for Gastroenterology, Hepatology and Endoscopy. 2019 May;1(3):100–7.**

5. **Berman P, Futoran K, Lewitus GM, Mukha D, Benami M, Shlomi T, et al. A new ESI-LC/MS approach for comprehensive metabolic profiling of phytocannabinoids in Cannabis. Sci Rep. 2018 Sep 24;8(1):14280.**

6. **Amin MR, Ali DW. Pharmacology of medical cannabis. Adv Exp Med Biol. 2019;1162:151–65.**

7. **Lewis MA, Russo EB, Smith KM. Pharmacological foundations of cannabis chemovars. Planta Med. 2018 Mar;84(4):225–33.**

8. **Grotenhermen F, Müller-Vahl K. Medicinal uses of marijuana and cannabinoids. CRC Crit Rev Plant Sci. 2016 Nov;35(5-6):378–405.**

9. **Naftali T, Bar-Lev Schleider L, Dotan I, Lansky EP, Sklerovsky Benjaminov F, Konikoff FM. Cannabis induces a clinical response in patients with Crohn's disease: a prospective placebo-controlled study. Clin Gastroenterol Hepatol. 2013 Oct;11(10):1276–1280.e1.**

10. **Altman DG, Bland JM. How to randomise. BMJ. 1999 Sep 11;319(7211):703–4.**

11. **Baram L, Peled E, Berman P, Yellin B, Besser E, Benami M, et al. The heterogeneity and complexity of Cannabis extracts as antitumor agents. Oncotarget. 2019 Jun 25;10(41):4091–106.**

12. **Milay L, Berman P, Shapira A, Guberman O, Meiri D. Metabolic profiling of cannabis secondary metabolites for evaluation of optimal postharvest storage conditions. Front Plant Sci. 2020 Oct 15;11:583605.**

13. **Lucas CJ, Galettis P, Schneider J. The pharmacokinetics and the pharmacodynamics of cannabinoids. Br J Clin Pharmacol. 2018 Aug 7;84(11):2477–82.**

14. **Knowles SR, Keefer L, Wilding H, Hewitt C, Graff LA, Mikocka-Walus A. Quality of Life in Inflammatory Bowel Disease: A Systematic Review and Meta-analyses-Part II. Inflamm Bowel Dis. 2018 Apr 23;24(5):966–76.**

15. **Khanna R, Nelson SA, Feagan BG, D'Haens G, Sandborn WJ, Zou GY, et al. Endoscopic scoring indices for evaluation of disease activity in Crohn's disease. Cochrane Database Syst Rev. 2016 Aug 8;(8):CD010642.**

16. **Daperno M, D'Haens G, Van Assche G, Baert F, Bulois P, Maunoury V, et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. Gastrointest Endosc. 2004 Oct;60(4):505–12.**

17. **Association, Psychiatric A. Diagnostic and statistical manual of mental disorders2013 ..**

18. **Naftali T, Bar-Lev Schleider L, Sklerovsky Benjaminov F, Lish I, Konikoff FM, Ringel Y. Medical cannabis for inflammatory bowel disease: real-life experience of mode of consumption and assessment of side-effects. Eur J Gastroenterol Hepatol. 2019 Nov;31(11):1376–81.**

19. **Benson MJ, Abelev SV, Connor SJ, Corte CJ, Martin LJ, Gold LK, et al. Medicinal cannabis for inflammatory bowel disease: A survey of perspectives, experiences, and current use in australian patients. Crohns Colitis 360. 2020 Apr 1;2(2).**

20. **Cohen L, Neuman MG. Cannabis and the gastrointestinal tract. J Pharm Pharm Sci. 2020;23:301–13.**

21. **Irving PM, Iqbal T, Nwokolo C, Subramanian S, Bloom S, Prasad N, et al. A Randomized, Double-blind, Placebo-controlled, Parallel-group, Pilot Study of Cannabidiol-rich Botanical Extract in the Symptomatic Treatment of Ulcerative Colitis. Inflamm Bowel Dis. 2018 Mar 19;24(4):714–24.**

22. **Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez AV, et al. Cannabinoids for Medical Use: A Systematic Review and Meta-analysis. JAMA. 2015 Jun 30;313(24):2456–73.**

23. **Mbachi C, Attar B, Oyenubi O, Yuchen W, Efesomwan A, Paintsil I, et al. Association between cannabis use and complications related to ulcerative colitis in hospitalized patients: A propensity matched retrospective cohort study. Medicine. 2019;98(32):e16551.**

24. **Mbachi C, Attar B, Wang Y, Paintsil I, Mba B, Fugar S, et al. Association between cannabis use and complications related to crohn's disease: A retrospective cohort study. Dig Dis Sci. 2019 Mar 2;64(10):2939–44.**

25. **Jamontt JM, Molleman A, Pertwee RG, Parsons ME. The effects of Delta-tetrahydrocannabinol and cannabidiol alone and in combination on damage, inflammation and in vitro motility disturbances in rat colitis. Br J Pharmacol. 2010 Jun;160(3):712–23.**

26. **Burstein S. Cannabidiol (CBD) and its analogs: a review of their effects on inflammation. Bioorg Med Chem. 2015 Apr 1;23(7):1377–85.**

27. **Mudge EM, Brown PN, Murch SJ. The Terroir of Cannabis: Terpene Metabolomics as a Tool to Understand Cannabis sativa Selections. Planta Med. 2019 Jul;85(9-10):781–96.**

494

495 Legends

496 Figure 1: composition of the Cannabis oil used in the study

497 Figure 2: Plasma levels of THC and CBD following asingle mean oral dose of
498 cannabis extract containing 7.5 mg CBD and 2 mg THC.

499 **Table 1: Patient demographics**

500 **Table 2: Medical treatment before and during the study**

501 **Table 3: Clinical, laboratory and endoscopy results**

502 **Table 4: Within-group analysis of change of parameters between visits 1-3**

503 **Table 5: Adverse effects of treatment**

504

505

506

507

508

509

510

511 **Table 1: Patient demographics**

Variable	**Cannabis extract N=30**	**Placebo N=26**	**P-value**
Age, years median (IQR)	28 (24-38)	33 (27-43)	0.274
Sex (M/F)	10/20	16/10	0.035
Disease duration, years median (IQR)	5 (2-11)	9 (5-15)	0.062
Current smoking	5	2	0.46
IBD in family	12	14	0.30

512

513 **Table 2: Medical treatment before and during the study**

514

Treatment	Past			Present		
	Cannabis	Placebo	P-value	Cannabis	Placebo	P-value
5 ASA	21 (70%)	21 (80%)	0.353	3 (10%)	5 (19%)	0.451
Antibiotics	9(30%)	4(16%)	0.224	0	1(4%)	0.464
Steroids	25 (83%)	18 (70%)	0.20	6 (20%)	2(8%)	0.263
Immuno-modulators	20 (65%)	17 (66%)	0.92	8 (26%)	4 (15%)	0.305
Biologics	15 (50%)	15 (57%)	0.565	8 (26%)	7 (26%)	0.983

515

516

517 **Table 3: Clinical, laboratory and endoscopy results**

518

Visit 1 Median (IQR)				**Visit 3** Median (IQR)			
Variable	Cannabis N=30	Placebo N=26	P-value	Cannabis N=30	Placebo N=26	P-value	P-value*
CDAI score	282 (243-342)	264 (234-320)	0.60	166 (82-226)	237 (121-271)	0.038	0.072
Bowel movements/day	5 (3-7)	5 (3-8)	0.50	2.5 (1-4)	3 (1.5-7.5)	0.233	0.77
Abdominal pain	2 (1.25-2)	2 (1.75-2)	0.81	1 (0-2)	2 (0-2)	0.082	0.078
Weight (kg)	62 (56-77)	63 (52-78)	0.85	62 (55-74)	64 (51-78)	0.92	0.57
QOL	74 (65-87)	74 (57-82)	0.67	91 (85-102)	75 (69-88)	0.004	0.143
Calprotectin (µg/g)	139 (64-300)	112 (50-185)	0.71	112 (65-300)	117 (50-300)	0.768	0.13
Hemoglobin, gr/dl	13±1.7	12±1.7	0.21	13±1.9	12±1.7	0.36	
CRP, mg/dl	1.4 (0.4-2.7)	1.7 (0.4-3.8)	0.50	1.3 (0.2-2.2)	1.5 (0.5-3)	0.385	0.54
SES score	10 (7-14)	11 (7-14)	0.79	7 (4-14)	8 (4-12)	0.75	0.185

519 *P-value for interaction, controlling for age, gender and illness duration

520

521 **Table 4: Within-group analysis of change of parameters between visits 1-3**

522

Variable	**Compound** **Δ visit 3-visit 1**	**P-value**	**Placebo** **Δ visit 3-visit 1**	**P-value**
CDAI score	-3.87	<0.001	-2.94	0.003
Bowel movements/day	-3.04	0.002	-2.7	0.007
Abdominal pain	-3.57	<0.001	-1.27	0.2
Weight	-4.3	0.66	-5.87	0.55
QOL	-3.03	0.002	-1.71	0.08
Calprotectin	-0.66	0.50	-0.41	0.79
CRP, mg/dl	-0.71	0.47	-0.41	0.57
SES score	-1.46	0.14	-3.22	0.001

523

524

525

526 **Table 5: Adverse effects of treatment**

Variable	**Cannabis (Y/N)**	**% Yes**	**Placebo (Y/N)**	**% Yes**	**p-value**
Visual distortion	3/17	15%	0/20	0%	0.231
Restlessness	1/19	5%	2/18	10%	>0.999
Behavioral change	3/17	15%	1/19	5%	0.60
Confusion	4/16	20%	0/20	0%	0.10
Decreased memory	6/14	30%	1/19	5%	0.091
Dizziness	5/15	25%	2/18	10%	0.40
Cough	0/20	0%	0/20	0%	>0.999
Shortness of breath	0/20	0%	0/21	0%	>0.999
Difficulty stopping use	0/21	0%	1/19	5%	0.48

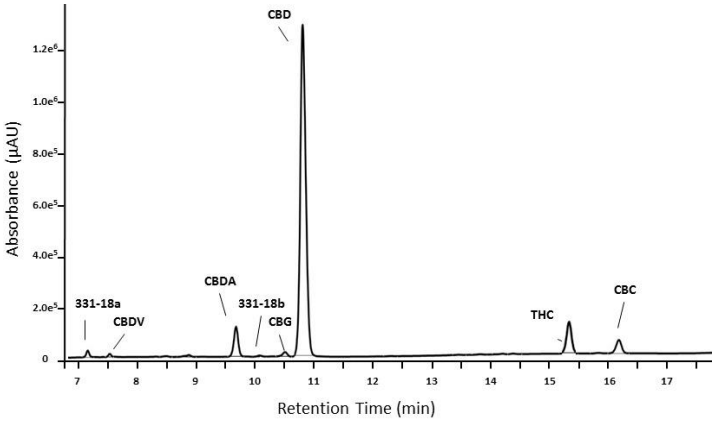
527

528

A

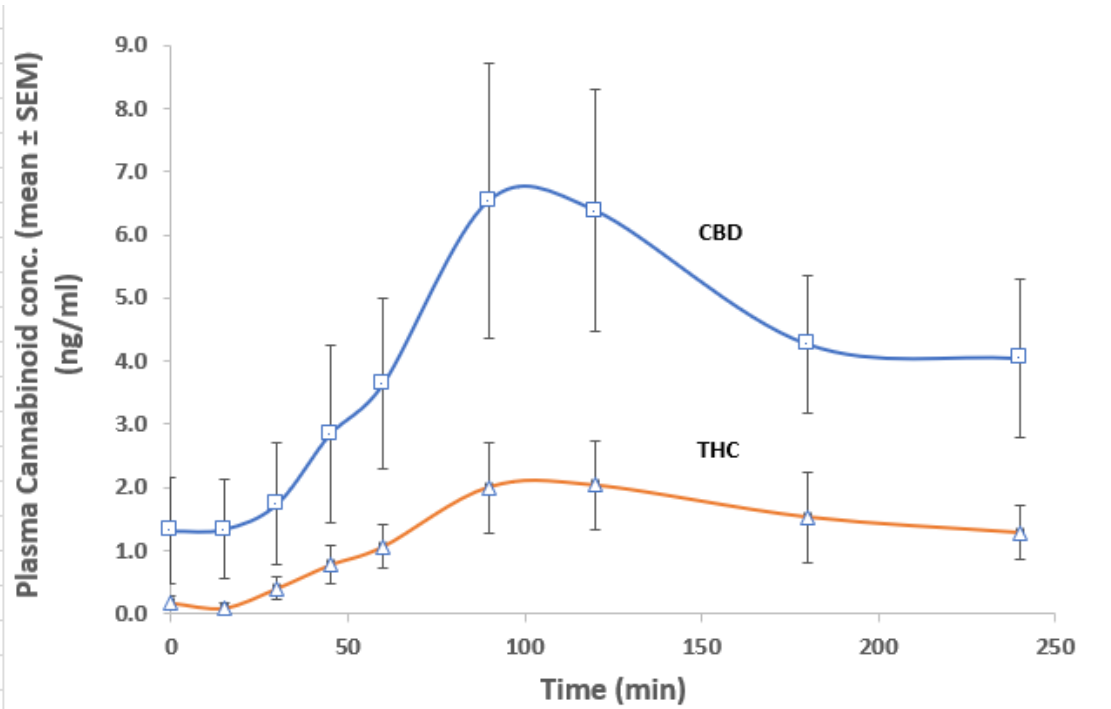
Phytocannabinoid	% w/w
CBD	15.3302
THC	4.0128
CBDA	0.9145
CBC	0.7257
331-18a	0.3401
CBG	0.2113
331-18b	0.1023
327-13c	0.0984
313-16b	0.0818
CBDV	0.0653
CBD-C4	0.0496
CBCA	0.0465
CBE	0.0443
373-15c	0.0312
331-18d	0.0294
327-13a	0.0276
329-11c	0.0155
CBN	0.0125
CBGA	0.0096
CBDO	0.0089
CBDM	0.0064
CBDVA	0.0063
329-11a	0.0057
CBT-1	0.0053
CBL	0.0052
CBC-C4	0.0046
CBT-3	0.0045
357-16a	0.0043
CBDA-C4	0.0038
CBEA	0.0035
CBT-2	0.0034
331-18c	0.0034
373-15b	0.0030
Sesqui-CBG	0.0028
371-14a	0.0021
CBND	0.0019
329-11d	0.0016
CBCO	0.0014
375-19a	0.0013
CBDOA	0.0011
CBCVA	0.0004
CBNDA	0.0002

B



Phytocannabinoid profiling of Avidekel cannabis oil by ESI-LC/MS. Peaks were identified according to an in-house LC/MS/MS spectra library of phytocannabinoids.
(A) Heat map of phytocannabinoid peaks areas of Avidekel oil presented as % w/w. Phytocannabinoids peaks that were less than 0.0001 are not presented.
(B) Total ion chromatogram (TIC) of Avidekel oil.

Figure 1: composition of the Cannabis oil used in the study



Parameter	Tlag±SD	Cmax±SD	Tmax±SD	T½,abs	$AUC_{0\ to\ infinity}$
CBD	55±54	8.1±5.4	102±16	39±25	2419±1539
THC	63±63	3.0±2.1	108±45	33±16	643±134
Units	min.	ng/ml	min.	min.	(ng/ml)*min

Figure 2: Plasma levels of THC and CBD following asingle mean oral dose of cannabis extract containing 7.5 mg CBD and 2 mg THC.