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Original Article

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Oral CBD-rich Cannabis Induces Clinical but Not Endoscopic Response in Patients with Crohn's Disease, a Randomised Controlled Trial

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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, randomised, placebo-controlled, single-centre trial, patients received orally either cannabis oil containing160/40 mg/ml cannabidiol/tetrahydrocannabinol [CBD/THC] or placebo for 8 weeks. Disease parameters, including the 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%],30 in cannabis and 26 in placebo groups. CDAI at recruitment and after 8 weeks was 282 (interquartile range [IQR] 243-342) 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 quality of life [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 [IQR 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 (C-reactive protein [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.

Key Words: Crohn's disease; cannabis; cannabidiol

1. Introduction

Despite the extensive progress made in the treatment of Crohns disease [CD] in the past 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 inflammatory bowel disease [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-tetrahydrocannabinol [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 analyse 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,[10] 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.

2. Materials and Methods

2.1. Study design

We conducted a single-centre, prospective, randomised, 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 2-week screening period to evaluate for baseline symptoms, an 8-week treatment period, and a 2-week follow-up period after the treatment was discontinued.

Patients were evaluated by medical interview, physical examination, and blood and stool tests at baseline [end of screening; Week 0] and after 2 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 8 weeks of treatment. Primary outcome was defined as a statistically significant reduction in Crohn's Disease Activity Index [CDAI] and improvement in quality of life [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 C-reactive protein [CRP] and calprotectin, and improvement of at least 30 points in quality of life as measured by the short-form -36 [SF 36].

2.2. Blinding and randomization

Patients were randomly assigned using a block method in blocks of five in a 1:1 ratio to receive either high-CBD cannabis oil or placebo.[11] The study compound was prepared and randomised in the Tikun-Olam 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.

2.3. Study population

The study population included male and female patients ages 20 to 80 years, with mild-to-moderate CD diagnosed at least 3 months before enrolment. Disease activity was determined by the 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 4 weeks for 5-aminosalicylates [5-ASAs] or 3 months for immunomodulators and biologic treatments. Steroids were permitted at a maximal dose of 20 mg prednisone and if the patients were on a stable dose for at least 8 weeks before enrolment. 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, and 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.

2.4. 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 full details of composition see Figure 1. Patients in the control group received placebo oil containing olive oil and chlorophyll so that it looked and smelt similar.

The oil used in the study was analysed 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 available at *ECCO-JCC* online.[5,12,13]

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

Patients were instructed to instol 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 diarrhoea] 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.[14]

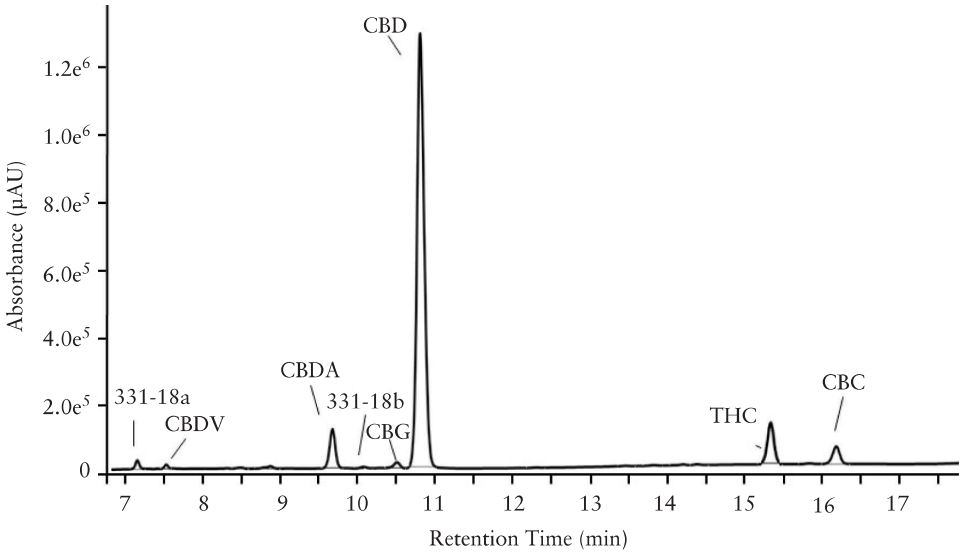
2.5. Pharmacokinetic study

A subgroup of seven patients participated in the pharmacokinetic study. Blood samples for THC and CBD levels were drawn before and 10, 20, 60, 120, 180, and 240 min 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], a laboratory accredited 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.

A

Phytocannabinoid	% w/w
CBD	15.3102
THC	4.0128
CBDA	0.9145
CBC	0.7237
331-18a	0.3431
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.

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 slope 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.

2.6. 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 comorbidity, if any], CD history, past and present medications, family history of IBD, and results of recent blood tests and endoscopic and imaging studies.

For clinical assessment we used the CDAI, as well as additional subanalyses 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 [SF-36].[10] 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].

2.7. 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]

2.8. 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, behavioural change, confusion, decreased memory, dizziness, cough, and shortness of breath.

2.9. Statistical analysis

Categorical variables were reported as number and percentage. Continuous variables were evaluated for normal distribution using histograms and QQ plots. Baseline characteristics at first visit and third visit evaluation were compared between groups using independent sample t -tests or Mann-Whitney tests for continuous and ordinal variables, and chi square tests or Fisher's exact tests were used for categorical variables. In each group, differences between the first and third visits were tested using paired sample t tests or

Wilcoxon tests for continuous and ordinal variables. Generalised 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 two-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].

2.10. 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.

3. Results

3.1. 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, and 13 were in endoscopic remission at colonoscopy [including terminal ileum]. Other reasons for non-recruitment were [one patient each] breastfeeding, 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.

3.2. Dosing and pharmacokinetics

Patients started with a dose of 2 drops a day, equivalent to 16 mg CBD and 4 mg 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 80 mg CBD [IQR 52–108] and 20 mgTHC [IQR 13–27].Seven patients were included in the pharmacokinetics study. Following oral administration of the study extract, for CBD the mean T_{lag} was 55 ± 54 min, mean C_{max} was 8.1 ± 5.4 ng/ml, mean T_{max} was 102 ± 16 min, $T_{½,abs}$ was 39 ± 25 min, and $AUC_{0\rightarrow infinity}$ was 2419 ± 1539 [ng/ml]*min. For THC the mean T_{lag} ± standard deviation [SD] was 63 ± 63 min, mean C_{max} was 3.0 ± 2.1, mean T_{max} was 108 ± 45 min, $T_{½,abs}$ was 33 ± 16 min, and $AUC_{0\rightarrow infinity}$ was 643 ± 134 ng/ml*min, as depicted in Figure 2. As depicted in Figure 2, the oral delivery of CBD and THC is characterised by a latency period of 1 h followingdelivery, slow absorption and low CBD and THC peak plasma concentrations occurring within about 2 h.

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

IQR, interquartile range; M/F, male/female.

3.3. 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] vs75 [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].

3.4. 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 cut-off of 100 µg/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.

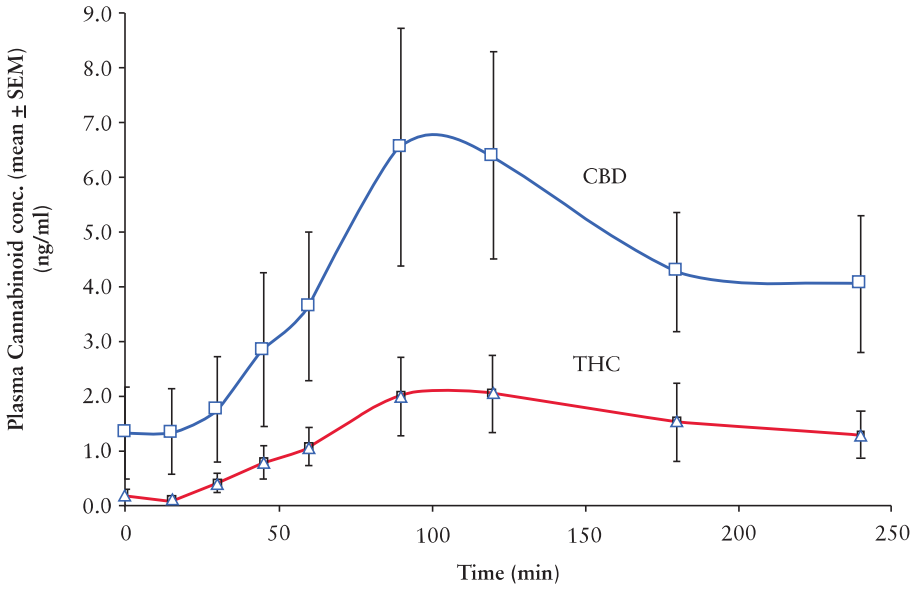
Normalisation after 8 weeks of initially high CRP was observed in five patients of the study group but only in one in the placebo group. In two patients in the placebo group, CRP was normal at the beginning of the study but was elevated after 8 weeks of treatment. In three patients in the study group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

Table 2. Medical treatment before and during the study

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
Immunomodulators	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

5-ASA, 5-aminosalicylic acid.



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 ofTHC and CBD following a single mean oral dose of cannabis extract containing 7.5 mg CBD and 2 mgTHC.THC, Δ9-tetra-hydrocannabinol; CBD, cannabidiol.

3.5. 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 2 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, available at *ECCO-JCC* online].

Patients were also specifically asked whether they experienced any adverse effects, such as visual distortion, restlessness, behavioural 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 in stopping the use [Table 5].

4. 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 were precisely analysed and blood levels were checked. Our study met the predetermined endpoints in terms of clinical and QOL improvement, but did not meet the endpoint of 30 points' improvement in QOL or of 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 [Table 3]. When normalised for age, gender, and illness duration, the between-group differences in QOL were no longer significant. Improvement in sleep, pain, abdominal swelling, appetite,

Table 3. Clinical, laboratory, and endoscopy results.

Visit 1				Visit 3			
Median [IQR]				Median [IQR]			
Variable	Cannabis	Placebo	*p*-value	Cannabis	Placebo	*p*-value	*p*-value*
	n = 30	*n* = 26		*n* = 30	*n* = 26		
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, g/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

IQR, interquartile range; CDAI, Crohn's Disease Activity Index; QOL, quality of life; CRP, C-reactive protein; SES, Simple Endoscopic Score.
**p*-value for interaction, controlling for age, gender, and illness duration.

Table 4. Within-group analysis of change of parameters between visits 1–3.

Variable	Compound	*p*-value	Placebo	*p*-value
	Δ visit 3-visit 1		Δ visit 3-visit 1	
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

CDAI, Crohn's Disease Activity Index; QOL, quality of life; CRP, C-reactive protein; SES, Simple Endoscopic Score.

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
Behavioural 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

Y/N, yes/no.

and general well-being, all important parameters contributing to patients' well-being, was significantly more pronounced in the extract-treated group. It is worth noting that symptomatic improvement in the study group was immediate, whereas if it occurred in the placebo group it was only after 2 weeks. Moreover, the placebo group consumed a larger volume of the study compound, presumably because they did not experience any beneficial or side effects.

The potential benefits of cannabis for treating different diseases including IBD have been of great interest, but the evidence supporting it is very limited. Unfortunately, most studies regarding cannabis use in IBD are descriptive or limited to reports on prevalence of use[2,3,19] with very limited data about the dose, mode of consumption, and efficacy. It is particularly challenging to perform cannabis studies because of the difficulty in creating a placebo and the huge variety of cannabis plants, as well as the status of cannabis as an illicit drug.[20] In this study, we tried to overcome these obstacles by using well-controlled cannabis content. We used the specific Avidekel strain with a known composition of both cannabinoids and terpenes. Terpenes may have a synergistic therapeutic effect,[21] so analysing their composition is important to identify those that contribute to the effect of cannabis.

In addition the cannabis was consumed orally, thus avoiding exposure to noxious pyrolytic by-products produced by smoking. The combination of high-CBD and low-THC cannabis together with oral consumption results in reduced psychotropic effects, longer absorption time, and increased local direct interaction of the cannabinoids with the target site. We used the 'start low, go slow, and stay low' approach, carefully observing the patient for desired and adverse effects,[16] an approach that originated from the limited availability of applicable pharmacokinetic and pharmacodynamic information and was also used in other studies.[22]

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 and human studies of IBD, which showed decreased inflammation.[22–24] 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 another composition could achieve better results. However, improvement in symptoms is an important therapeutic goal, and in the appropriate circumstances, addition of cannabis could help patients cope with the burden of disease.

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, whereas 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.

In the present study in CD patients, we observed plasma concentration-time profiles of CBD and THC similar to those reported in other studies, demonstrating that despite small intestinal pathology in CD, cannabis absorption is not altered.[27] It is worthwhile noting the high inter-individual variations in the pharmacokinetic parameters following oral intake of CBD and THC, indeed in several studies, $C_{max}$was observed as late as 4 and even 6 h.[28,29] This could be due to multiple factors such as erratic absorption, poor oral bioavailability [estimated to be as low as 6%], 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 to 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 is well absorbed, well tolerated, and can induce symptomatic improvement in patients with mild-to-moderate CD without significant changes in inflammatory markers or endoscopic scores. Hence, although 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.

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

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Conflict of Interest

LBS is an employee of Tikun-OlamCannbit Pharmaceuticals, a cannabis manufacturing company. All other authors have no conflict to declare.

Author Contributions

TN: study design, patient recruitment, data collection and data analysis, and writing the first draft of the paper. L BS: study design, preparation of study compound, critical revision of the article. SA: pharmacokinetic analysis, literature search analysis and interpretation of data, figures, critical revision of the article. DM: analysis of the study compound, analysis and interpretation of data, figures, critical revision of the article. FMK: study design, patient recruitment, critical revision of the article. All authors have approved the final draft submitted.

Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

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