Original Article

Therapeutic Effects of Cannabinoids on Ulcerative Colitis: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Abstract:

Objective: This study aimed to perform a meta-analysis to ascertain the efficacy and safety of Cannabis in treating ulcerative colitis (UC).

Material and Methods: A meta-analysis of randomized controlled trials (RCTs) included in three databases (PubMed, Google Scholar and Science Direct) was performed; from inception till 31st July 2023, so as to ascertain the efficacy and safety of Cannabis in UC. Primary outcomes included: disease activity and endoscopic indices, and quality of life (QOL). The risk of bias in the studies was assessed via the RoB2 tool.

Results: In total 1,928 records identified; of which four were eligible for inclusion. The risk of bias in the included studies was moderate. The patients were randomized to the cannabinoid group had significantly improved disease activity indices (standardized mean difference (SMD) –1.78; 95% confidence interval (CI) (–2.89 to 0.67); I^2=74%) and QOL (SMD –1.70; 95% CI (0.24 to 3.17); I^2=75%) than those in the placebo group. However, cannabinoids did not have a significant impact on endoscopic indices (SMD –0.40; 95% CI (–0.92 to 0.11); I^2=0%) nor C-reactive protein (CRP) levels (SMD –0.49; 95% CI (–0.87 to 1.85); I^2=85%) of UC patients.

Conclusion: Cannabinoids show potential in improving disease activity and QOL; however, their impact on endoscopic indices and CRP levels remains inconclusive.

Keywords: cannabinoids, disease activity score, endoscopic score, QOL, ulcerative colitis

Introduction

Ulcerative colitis (UC) is an inflammatory bowel disease (IBD), with alternating periods of remission and flare. It is characterized by abdominal pain, weight loss, diarrhea with mucus and/or blood, and some extra-intestinal symptoms; such as arthritis and uveitis. Inflammatory bowel disease has been on the rise in the last few decades, and is currently one of the most common autoimmune diseases[1-5]. A combination of clinical, endoscopic, biochemical, histo-logical, and stool investigations are required to evaluate UC patients[6]. However, the commonly employed scoring systems are the Disease Activity Index, Lichtiger score and the Mayo score[7]. Current strategies suggest working towards remission in all parameters (endoscopic, clinical, biochemical, and histological) to allow for a better quality of life (QOL) as well as long and complete remission[8,9]. This includes pain management, reduction in bowel movements and other symptom controls, as inadequate symptom control can have both disastrous social and psychological consequences for patients experiencing chronic and severe pain and impact all disease activity scores[10].

Even after standard therapies (Mesalamine, Azathioprine, Methotrexate, Corticosteroids), adjunctive therapies (Vitamin D, probiotics), and newer options; such as biologics, the ultimate goal of reaching clinical remission in UC patients is still elusive, wherein, a 30% to 40% loss of response rate is especially worrisome[11-14]. Moreover, adverse events (AEs) with standard immunosuppressive therapies (sensitivity reactions, opportunistic infections etc.) often complicate the care of IBD patients[15]. The most debilitating fact for the patients is that, more often than not, abdominal pain and discomfort persist even when the patient is clinically in remission. Therefore, many patients desperately search for alternative medications; particularly for pain control and bowel movements[16].

Cannabis has been used recreationally and medicinally for many years, inhaled via cigarettes or vaporizers, orally in beverages, pills, and sublingual oils[17]. Recently, cannabinoids have been proposed in UC patients as a supportive therapy, particularly for pain control. A greater frequency, higher dosage and earlier onset of cannabis usage have been noted in IBD patients compared to healthy controls: off late[18,19]. Multiple mechanistic reasons corroborate the role of cannabinoids in UC. The anti-inflammatory properties of cannabinoids have been well-established in vitro and in animal models. However, it is unclear whether cannabinoids can impact the underlying inflammatory pathology in UC[20,21]. The benefits of cannabinoids in UC occur due to their interaction with the extended endocannabinoid system also in addition to complex modulation of the G-protein-coupled receptors (GPR), cannabinoid receptor 1 (CB1), and 2 (CB2), Transient receptor potential vanilloid 1 receptor (TRPV1), peroxisome proliferator-activated receptor alpha receptors and the orphan G-protein coupled receptors, GPR55 and GPR119[22]. Additionally, cannabinoids attenuate gastro-intestinal motility and visceral hypersensitivity through CB1 activation in pre-synaptic neurons and downregulation of TRPV1 channels[23,24]. Furthermore, there have been a few studies that have explored the potential of cannabinoids in chemotherapy-induced mucositis and wound-induced ulcers[25,26].

Two systematic reviews without pooling of results, and two meta-analyses with high heterogeneity (with both observational and interventional studies) have already been performed to assess the efficacy and safety of cannabinoids in UC[27-30]. However, results have been conflicting. Hence, this systematic review and meta-analysis aimed to include all RCTs that have both well-defined outcomes, and evaluated the efficacy and safety of cannabinoids in UC.

Material and Methods

This systematic review and meta-analysis were based on the guidelines in the Cochrane handbook for systematic reviews of interventions[31], and described according to Preferred Reporting Items for Systematic Reviews and Meta Analysis (PRISMA) statement[32].

The protocol was designed a-priori and registered in PROSPERO (CRD42023392445).

Setting

In the systematic review part of the study, only randomized controlled trials (RCTs) were included. However, RCTs with similar outcomes were chosen in the meta analysis part of the study.

Inclusion and exclusion criteria: only RCTs comparing any formulation, route, duration and dose of Cannabinoids with a placebo in patients of UC were included. Studies not including RCTs were excluded (e.g., review articles, observational studies, book chapters, case reports, correspondence)

Primary outcomes

1. Disease activity improvement (disease activity score)

2. Mayo endoscopic score improvement

3. QOL improvement

Secondary outcomes

1. Percent of patients in clinical remission

2. Reduction in inflammatory markers

3. Reduction in abdominal pain severity

4. Reduction in the number of patients with blood in stool

5. Percent of adverse events

Search strategy

Three literature databases (PubMed, Google Scholar, and Science Direct) were searched, from the inception date to 31st July 2023. The reference lists of all suitable articles were screened to identify more relevant articles. There were no language restrictions. The search keywords included: cannabis OR cannabinoids OR cannabidiol OR tetrahydrocannabinol OR marijuana and inflammatory bowel disease OR UC.

Selection of studies

After searching the databases and removing duplicates, two authors (SS and RK) independently screened the titles/abstracts, using the relevant selection criteria. Full texts of the relevant articles were further evaluated, and VM was consulted to resolve any discrepancies.

Data extraction

Two authors (SS and RK) extracted data independently; according to inclusion criteria and pre-specified outcome measures. Articles published in a language other than English were removed. Any discrepancy in data handling or conflicts during data extraction were resolved through discussion with a third author (VM); as necessary.

Risk of bias evaluation of included studies

The cochrane risk of bias tool for randomized controlled studies was used for RCTs[31]. Three investigators (VM, RK, and SS) independently assessed the risk of bias with ROB2. Random sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, selective outcome reporting and other potential sources of bias were assessed. Each study was kept in a category of some concern, and low and high risk of bias.

Assessment of heterogeneity

Statistical heterogeneity was ascertained through the χ^2 test and I^2 statistics, using Review Manager Version 5.4. A visual inspection of outliers was also performed to

check for heterogeneity; due to the presence of outliers. If any outliers were identified, a sensitivity analysis was performed by the leave-one-out method.

Publication bias

The Funnel plot was used to check for the risk of bias through missing publications.

Statistical analysis

As all the data were continuous, a standardized mean difference with 95% CI was used Median values were converted into mean using appropriate software. As significant clinical heterogeneity was evident, the meta-analysis using the inverse variance method for continuous data was performed. To obtain a pooled result, the random effects model was applied[31].

Results

Included studies

There was a total oof four RCTs included in the analysis. Step-by-step method of inclusion and exclusion of studies is depicted in Figure 1. The details of the included studies are shown in Table 1[33–36].

The total number of participants in the analysis was 139, with ages ranging from 20–61. Of these 139 patients, 91 were male (65.4%). All the studies had a before and after comparison wherein, the baseline assessment was compared with the value after the intervention. One study was multicenter whereas, the rest were single-center studies. Outcomes were assessed using validated tools. Although the route and dose of cannabinoids differed in the studies (inhale in three studies and oral in one), they were primarily administered for eight weeks, except in one study where it was offered for ten weeks.

The study by Irving et al. could not be used for meta-analysis of any outcome, as they only reported treatment differences and did not report actual values.

Risk of bias for included studies

Rhe RoB 2.0 tool for RCTs was used to evaluate the risk of bias in the studies. Overall, two studies had Low risk (Neftali et al. 2021 and Irving et al. 2018); although, the study by Metalon et al. 2021, was associated with a high risk of bias. There was some concern in the study by Neftali et al. 2018: RoB results are shown in Figures 2A and 2B.

Disease activity reduction in patients of ulcerative colitis on cannabinoids vs placebo
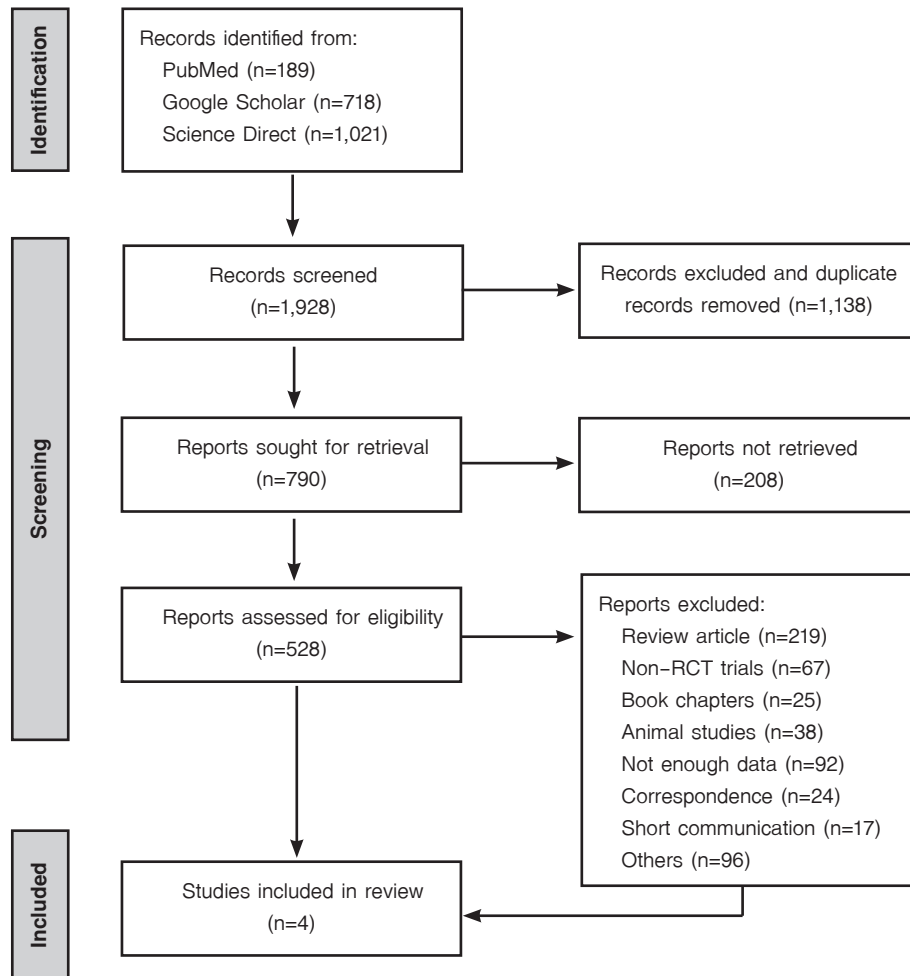
The pooled result showed a significant difference in disease activity reduction between both groups (standardized mean difference –1.78; 95% CI (–2.89 to –0.67); I^2=74%).), over eight weeks. Data are shown in Figure 3A: no significant publication bias was seen (Figure 3B).

Sensitivity analysis

As there was a high risk of bias and heterogeneity in the study by Metalon et al. 2021[34], a sensitivity analysis (leave one out method) was performed by removing the offending research from the data analysis. The disease activity reduction across the groups remained significantly different (standardized mean difference –1.21; 95% CI (–1.77 to –0.65); I^2=0%). Data are shown in Figure 4A: no significant publication bias was seen (Figure 4B).

Mayo endoscopic score reduction in patients of ulcerative colitis on cannabinoids vs placebo

The pooled result showed a non-significant difference in the Mayo endoscopic score reduction between both groups (standardized mean difference –0.40; 95% CI (–0.92 to 0.11); I^2=0%) over eight weeks. Data are shown in Figure 5A.

Figure 1 Flow chart of study selection process

QOL improvement in patients of ulcerative colitis on cannabinoids vs placebo

The pooled result showed a significant difference in the QOL improvement between both groups (standardized mean difference 1.70; 95% CI (0.24 to 3.17); I^2=75%) over eight weeks. Data are shown in Figure 5B.

Clinical remission in patients of ulcerative colitis on cannabinoids vs placebo

Only one study reported the % of patients in clinical remission. In the study by Irving et al. 2018[36], 41% of patients achieved clinical remission in the treatment group compared to 30% in the placebo group.

Table 1 Characteristics of included studies

Author	Design (duration)	Sample characteristics	Intervention	Control	Outcome/ measures	Results	Side effects/ adverse events	Main conclusion
Naftali et al. 2021[33] Israel	Single-center, prospective, randomized, double–blind, placebo–controlled, parallel–arm clinical study NCT01040910 2–week screening period to evaluate for baseline symptom, 8–week treatment period, and a 2–week follow–up period	32 (cannabis: 17, placebo: 15) Mean age: 30 y (26–40) Male: 18	Cigarettes containing 0.5 g of dried cannabis flowers with 80 mg Tetrahydro–cannabinol (THC) twice daily. Patients were required to start gradually, smoking half a cigarette (0.25g) in the first day and increasing by 0.25 g until a final dose of 0.5 g twice daily was reached	Placebo cigarettes contained cannabis flowers from which THC had been extracted, twice daily	The primary endpoint: –Improvement of the Lichtiger score Secondary end points were: –Quality of life (QOL). –Improvement of the Mayo endoscopic score. –Improvement of the bowel movements, abdominal pain –CRP, Calprotectin	Lichtiger index improved in the cannabis group from 10.9 (IQR 9–14) to 5 (IQR 1–7), (p-value<0.000), and in the placebo group from 11 (IQR 9–13) to 8 (IQR 7–10) (p-value=0.15, p between groups 0.001). QOL improved in the cannabis group from 77±4 to 98±20 (p-value=0.000) but not in the placebo group (78±3 at week 0 and 78±17 at week 8; p-value=0.459; p between groups 0.007). Mayo endoscopic score changed in the cannabis group from 2.13±1 to 1.25±2 (p-value=0.015) and in the placebo group from 2.15±1 to 1.69±1 (p-value=0.367, p between groups 0.17). Number of bowel movements per day decreased from 2.6 (IQR 2–4) to 1 (IQR 0–1, p-value<0.001) and from 2.6 (IQR 2–4) to 2 (IQR 2–3, p-value=0.168) in the active arm and placebo groups respectively (p between groups 0.006). Abdominal pain of ≥2 decreased from 10 (59%) at baseline to 1 (6%) after 8 weeks of treatment (p-value=0.006) in the cannabis group and from9 (60%) to 8 (55%), (p-value=0.429) in the placebo group, (p between groups=0.04). Number of patients who reported blood in stool decreased from 13 (76%) to 5 (30%) in the cannabis group (p-value=0.015) and from 9 (60%) to 6 (40%) in the placebo group (p-value=0.589) (p between groups=0.64).	The reported side effects were minor and did not lead to cessation of treatment in any patients There was no significant difference in side effects between both groups.	Short term treatment with THC rich cannabis induced clinical remission and improved QOL in patients with mild to moderately active ulcerative colitis. However, these beneficial clinical effects were not associated with significant improvement in the Mayo endoscopic score or laboratory markers for inflammation

Table 1 (continued)

Author	Design (duration)	Sample characteristics	Intervention	Control	Outcome/ measures	Results	Side effects/ adverse events	Main conclusion
						CRP, and fecal calprotectin did not change in both groups after 8 weeks. CRP–CBD: 1.8±0.2 to 2.8±1.9, p-value=0.652; placebo: 0.8±0.4 to 1.1±0.3, p-value=0.828 (p between groups=0.843) Calprotectin–CBD: 170±33 to 134±33, p-value=0.072; placebo: 226±34 to 218±67, p-value=0.9 (p between groups=0.393)		
Matalon et al. 2021[34] Israel	Randomized, placebo-controlled, double-blind controlled trial 8 weeks	UC patients: CBD (9), placebo (10) Age: CBD (40±16), placebo (34±9) Male: CBD (4/9), placebo (8/10)	UC patients: each cigarette contained 0.5 g of dried cannabis flowers equivalent to 11.5 mg of THC	Placebo: cigarettes contained cannabis flower from which THC had been extracted.	Disease activity index (Lichtiger score). Number of bowel movements per day (BM) QOL was assessed by using the SF36 questionnaire	Lichtiger score and QOL significantly improve in CBD group compared to placebo after treatment. Lichtiger score–(CBD: 9.7±1.2 to 4.9±1.06*, placebo: 11.6±0.9 to 8.4±0.9*^) BM–(CBD: 3.9±1.2 to 1.7±0.6*, placebo: 5.4±1.8 to 3.7±1.36*) QOL–(CBD: 72.7±6.7 to 98.2± 7.3*, placebo: 77.1±3.7 to 82± 4.7^) (*Results significantly different from visit 1 (p-value<0.05. ^ Results significantly different between the placebo to the cannabis group (p-value<0.05))	Not mentioned	Cannabis use affects eCB "tone" in UC patients and may have beneficial effects on disease symptoms in UC patients.

Author	Design (duration)	Sample characteristics	Intervention	Control	Outcome/ measures	Results	Side effects/ adverse events	Main conclusion
Naftali et al. 2018[35] Israel	Randomized, placebo–controlled Trial 8 weeks	28 patients Mean age: 33 (20–61) Males: 17	Two cigarettes daily, which contained 0.5 g of cannabis, corresponding to 11.5 mg THC.	Two cigarettes daily of placebo contained cannabis leaves from which THC was extracted.	Disease activity (DAI) Mayo Endoscopic Score Laboratory tests (CRP, Faecal Calprotectin)	DAI decreased from 10±3 to 4±3.2 and from 10±2.7 to 8±2 (p–value<0.01) in the THC and placebo groups, respectively Mayo endoscopic score decreased from a median of 2 (IQR=2–2.5) to 1 (IQR 0–2) (p–value=0.01) and from 2 (IQR=2–2) to 2 (IQR 1.25–2) (p–value=0.059) in the THC and placebo groups. Mean CRP changed from 0.8±0.9 to 0.7±1.2 and from 1.8 ±1.9 to 1±1.6 (mg/dl) (p–value=0.5) in the THC and placebo groups, respectively Faecal calprotectin changed from 135±113 to 115±103 and from 226±100 to 229±230 (mg/dl) in the THC and placebo groups, respectively (p–value=0.7).	No serious side effects were observed	Tetrahydro–cannabinol–rich cannabis is safe and can induce clinical as well as endoscopic improvement in moderately active UC
Irving et al. 2018[36] United Kingdom	Multicenter (9), randomized, double–blind, placebo–controlled, parallel–group study NCT01562314 12–week (1–week baseline, 10–week treatment period, 1–week follow–up)	60 (29: CBD, 31: placebo) Age CBD: 44.8±15.1 Placebo: 42.8± 12.9 Male: 23 (CBD), 21 (placebo)	Hard gelatin capsules containing 50 mg CBD–rich botanical extract in excipients twice daily by mouth, 30 minutes before morning and evening meals.	Matching placebo capsules containing excipients only.	Primary endpoint: –Percentage of patients in remission at the end of treatment, quantified as a Mayo score of ≤2 (with no subscore >1), after 10 weeks' treatment.	Primary endpoint was negative; end of treatment remission rates was similar for CBD–rich botanical extract (28%) and placebo (26%). Using the PP analysis set, there was agreater percentage of patients in remission in the CBD–rich botanical extract group: 7 (41%) patients, compared with 8 (30%) placebo patients, although the difference was not statistically significant (OR=1.30; 90% CI: 0.42–4.04; p–value=0.703). PP analyses of the more subjective physician's global assessment of illness severity, subject global impression of change, and patient–reported QOL outcomes (IBDQ score) were improved for patients taking CBD–rich botanical extract (p–value=0.069, p–value=0.003, and p–value=0.065, respectively).	All the UC patients in the Cannabinoid group suffered from AEs (29/29) compared to 77% (24/31) in the placebo group Treatment related AEs were reported (90%–CBD vs 48% placebo) Nervous system related AEs, more common with CBD–rich botanical extract.	Despite the poor tolerability of the active study medication and the relatively short treatment window, this study suggested that CBD–rich botanical extract may have provided therapeutic benefit to those patients who tolerated it.

Table 1 (continued)

Author	Design (duration)	Sample characteristics	Intervention	Control	Outcome/ measures	Results	Side effects/ adverse events	Main conclusion
			Following randomization, patients entered a 2-week dose escalation period during which they were required to reach their maximum tolerated dose of up to 250 mg (5 capsules) twice daily. Patients were then requested to maintain this dose for the remaining 8 weeks of the treatment period.		Secondary endpoints: −Physician global assessment of illness severity (PGAS) score −Subject global impression of change (SGIC) Inflammatory bowel disease questionnaire (IBDQ) score −Stool frequency and rectal bleeding on 4-point numerical rating scales (NRS) −Endoscopic sub score −Mayo score −Inflammatory marker levels (CRP, IL−2, IL−6, TNF−α, and faecal calprotectin); Safety endpoint	PGAS: (treatment difference= −0.50; 90% CI: −0.95 to −0.05; p-value=0.069) IBDQ: (treatment difference 25.3; 90% CI: 2.86−47.65; p-value=0.065) Stool frequency and rectal bleeding: improvements in both groups Rectal bleeding sub score: (−0.64: CBD vs −0.30 placebo for PP analysis) not statistically significant. Improvement in endoscopic sub score: CBD 14/21 (66.7%) vs placebo 10/26 (38.5%), p-value= 0.054 Mean mayo total scores: PP analysis favor CBD−rich botanical extract (treatment difference=−1.61; 90% CI: −3.06 to −0.17; p-value=0.068) Partial Mayo scores: PP analysis favored CBD−rich botanical extract (treatment difference=−1.53; 90% CI: −2.73 to −0.33; p-value=0.038) Faecal calprotectin (treatment difference=3.7; 90% CI:-116.8 to 124.2; p-value=0.959) Greater reductions in circulating inflammatory cytokines, associated with CBD−rich botanical extract, although none were statistically significant 21 patients withdrew, 15 of whom withdrew due to AEs: 10 in the CBD−rich botanical extract group, compared with 5 in the placebo group	AEs associated with possible disease progression including colitis, UC, and abdominal pain were all more prevalent in placebo (42%) than CBD−rich botanical extract (10%) Severe AEs: 3 (10%) patients on CBD−rich botanical extract developed severe neurological AEs (1 with disturbance in attention; 1 with dizziness; and 1 with dizziness, joint swelling, and muscle twitching), while 1 patient (3%) on placebo developed a severe gastrointestinal AE (haemorrhagic diarrhoea)	

CRP=C−reactive protein, IQR=interquartile range, UC=ulcerative colitis, CBD=cannabinoids, BM=bowel movements, SF36=Short Form Health Survey-36, AEs=adverse events, pp=per protocol
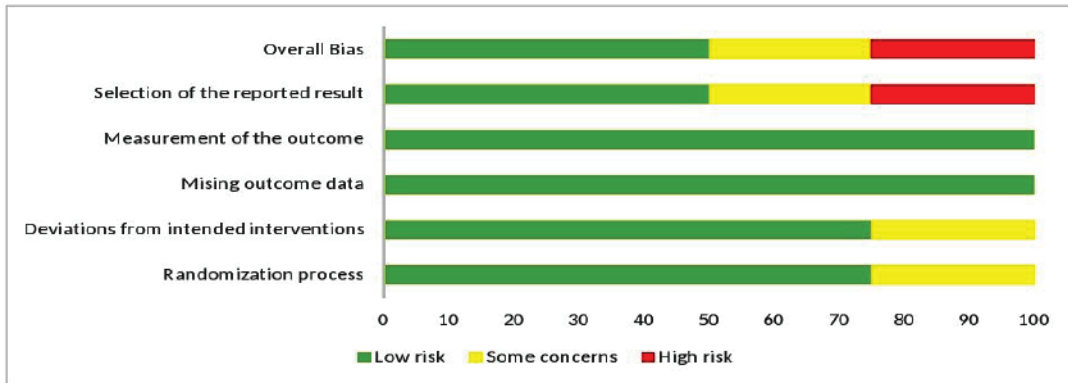
Figure 2A Quality assessment of retrieved studies

+=low risk of bias, !=some concerns, −=high risk of bias

Figure 2B RoB quality assessment of included studies
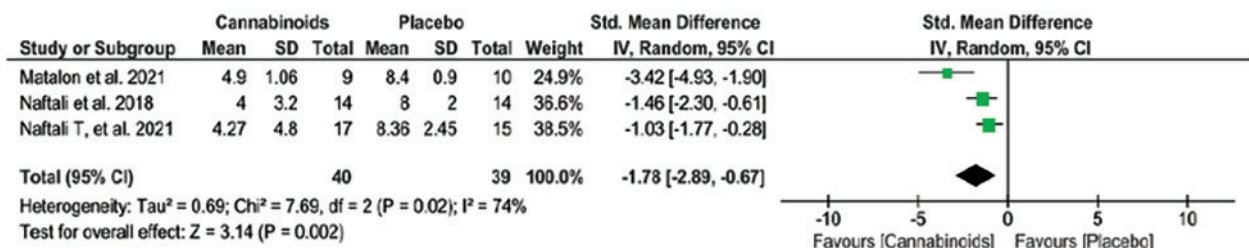
S.D.=standard deviation, std.=standardized, CI=confidence interval

Figure 3A Forest plot of disease activity reduction in patients of ulcerative colitis on cannabinoids vs placebo in randomized controlled trials; CI indicates confidence interval
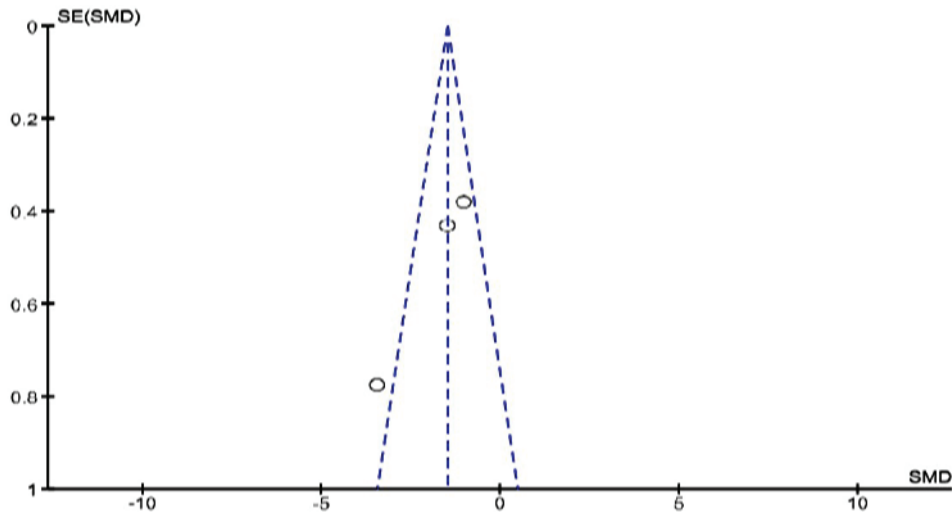
SE=standard error, SMD=standardized mean deviation

Figure 3B Funnel plot test of studies included in Figure 3A

S.D.=standard deviation, std.=standardized, CI=confidence interval

Figure 4A Forest plot of sensitivity analysis of disease activity reduction in patients of ulcerative colitis on cannabinoids vs placebo in randomized controlled trials; CI indicates confidence interval

SE=standard error, SMD=standardized mean deviation

Figure 4B Funnel plot test of studies included in Figure 4A

S.D.=standard deviation, std.=standardized, CI=confidence interval

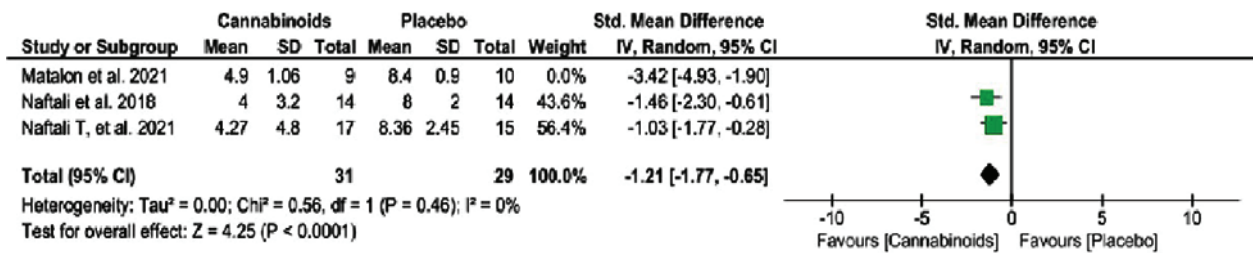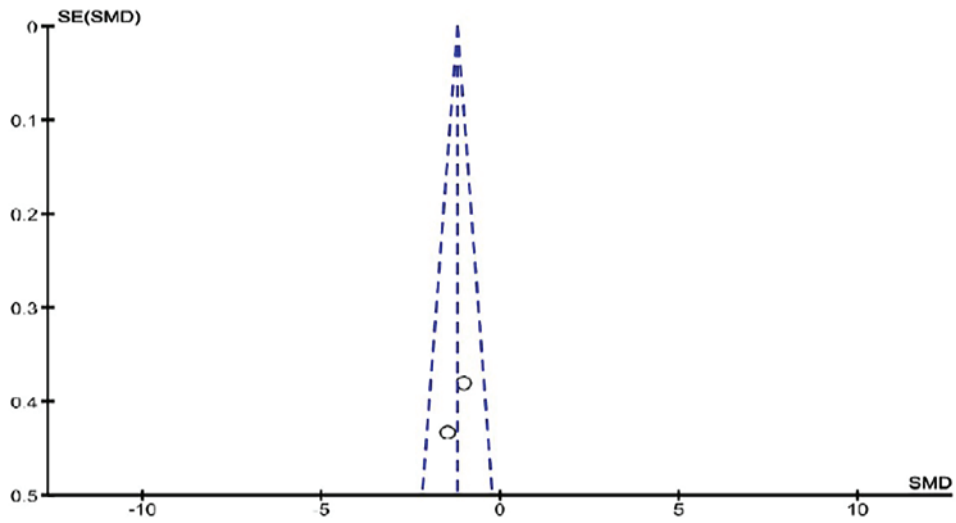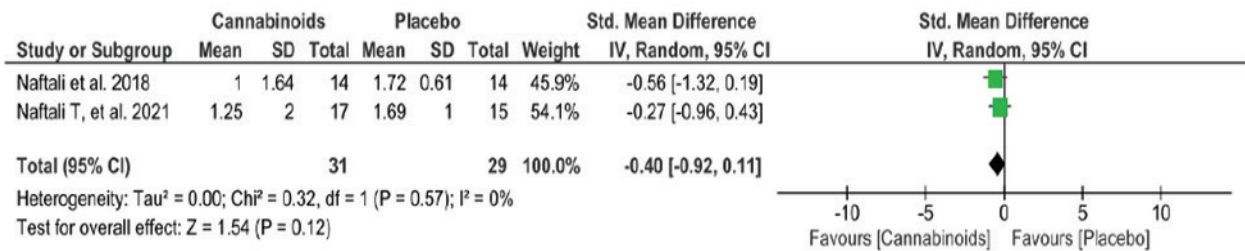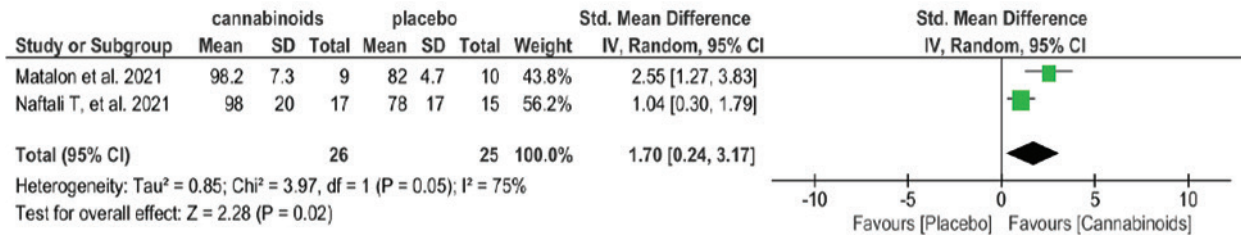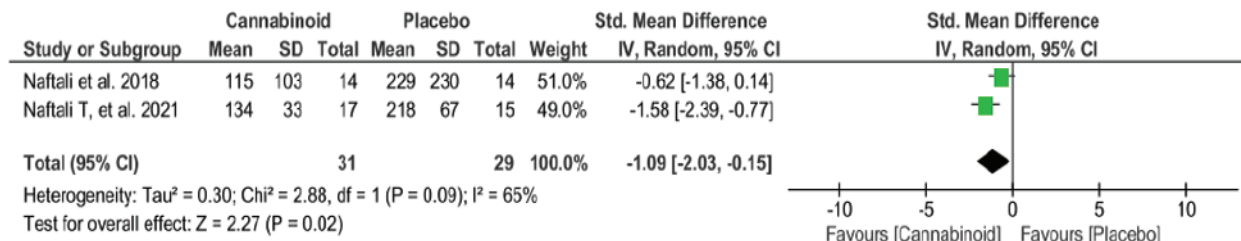**Figure 5A** Forest plot of Mayo endoscopic score reduction in patients of ulcerative colitis on cannabinoids vs placebo in randomized controlled trials; CI indicates confidence interval

| Study or Subgroup | cannabinoids | | | placebo | | | | Std. Mean Difference | |
	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	
Matalon et al. 2021	98.2	7.3	9	82	4.7	10	43.8%	2.55 [1.27, 3.83]	
Naftali T, et al. 2021	98	20	17	78	17	15	56.2%	1.04 [0.30, 1.79]	
Total (95% CI)			26			25	100.0%	1.70 [0.24, 3.17]	

Heterogeneity: Tau² = 0.85; Chi² = 3.97, df = 1 (P = 0.05); I² = 75%
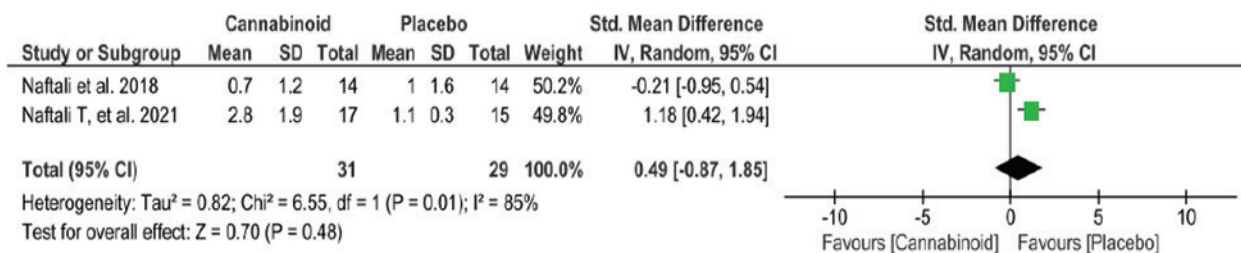Test for overall effect: Z = 2.28 (P = 0.02)

S.D.=standard deviation, std.=standardized, CI=confidence interval

Figure 5B Forest plot of quality of life improvement in patients of ulcerative colitis on cannabinoids vs placebo in randomized controlled trials; CI indicates confidence interval

| Study or Subgroup | Cannabinoid | | | Placebo | | | | Std. Mean Difference | |
	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	
Naftali et al. 2018	115	103	14	229	230	14	51.0%	-0.62 [-1.38, 0.14]	
Naftali T, et al. 2021	134	33	17	218	67	15	49.0%	-1.58 [-2.39, -0.77]	
Total (95% CI)			31			29	100.0%	-1.09 [-2.03, -0.15]	

Heterogeneity: Tau² = 0.30; Chi² = 2.88, df = 1 (P = 0.09); I² = 65%
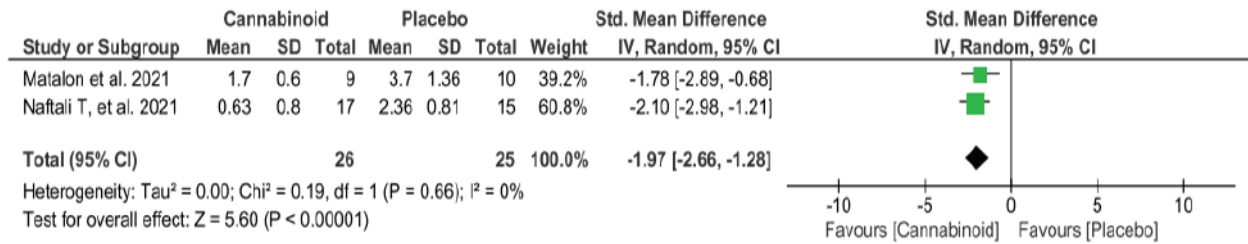Test for overall effect: Z = 2.27 (P = 0.02)

S.D.=standard deviation, std.=standardized, CI=confidence interval

Figure 6A Forest plot of calprotectin levels reduction in patients of ulcerative colitis on cannabinoids vs placebo in randomized controlled trials; CI indicates confidence interval

| Study or Subgroup | Cannabinoid | | | Placebo | | | | Std. Mean Difference | |
	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	
Naftali et al. 2018	0.7	1.2	14	1	1.6	14	50.2%	-0.21 [-0.95, 0.54]	
Naftali T, et al. 2021	2.8	1.9	17	1.1	0.3	15	49.8%	1.18 [0.42, 1.94]	
Total (95% CI)			31			29	100.0%	0.49 [-0.87, 1.85]	

Heterogeneity: Tau² = 0.82; Chi² = 6.55, df = 1 (P = 0.01); I² = 85%
Test for overall effect: Z = 0.70 (P = 0.48)

S.D.=standard deviation, std.=standardized, CI=confidence interval

Figure 6B Forest plot of CRP level reduction in patients of ulcerative colitis on cannabinoids vs placebo in randomized controlled trials; CI indicates confidence interval

Study or Subgroup	Cannabinoid			Placebo			Weight	Std. Mean Difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total		
Matalon et al. 2021	1.7	0.6	9	3.7	1.36	10	39.2%	-1.78 [-2.89, -0.68]
Naftali T, et al. 2021	0.63	0.8	17	2.36	0.81	15	60.8%	-2.10 [-2.98, -1.21]
Total (95% CI)			26			25	100.0%	-1.97 [-2.66, -1.28]

Heterogeneity: Tau² = 0.00; Chi² = 0.19, df = 1 (P = 0.66); I² = 0%
Test for overall effect: Z = 5.60 (P < 0.00001)

S.D.=standard deviation, std.=standardized, CI=confidence interval

Figure 6C Forest plot of decrease in the number of bowel movements in patients of ulcerative colitis on cannabinoids vs placebo in randomized controlled trials; CI indicates confidence interval

Calprotectin levels reduction in patients of ulcerative colitis on cannabinoids vs placebo

The pooled result showed a significant difference in the Calprotectin levels Reduction between both groups (standardized mean difference –1.09; 95% CI (–2.03 to –0.15); I²=65%); over eight weeks. Data are shown in Figure 6A.

CRP level reduction in patients of ulcerative colitis on cannabinoids vs placebo

The pooled result showed a non-significant difference in the CRP level reduction between both groups (standardized mean difference 0.49; 95% CI (–0.87 to 1.85); I²=85%); over eight weeks. Data are shown in Figure 6B.

Decrease in the number of bowel movements in patients of ulcerative colitis on cannabinoids vs placebo

The pooled result showed a significant difference in the Decrease in the number of bowel movements between both groups (standardized mean difference –1.97; 95% CI (–2.66 to –1.28); I²=0%); over eight weeks. Data are shown in Figure 6C.

Decrease in the number of patients with blood in stool in patients of ulcerative colitis on cannabinoids vs placebo

Only one study (Neftali et al. 2021)[33] had a non-significant difference in the number of patients with blood in stool across both groups; over eight weeks (p-value=0.645).

Decrease in the number of ulcerative colitis patients who reported severity of abdominal pain ≥2 on cannabinoids vs placebo

Only one study reported (Neftali et al. 2021)[33] a significant difference in the number of ulcerative colitis patients who reported severity of abdominal pain ≥2 across both groups; over eight weeks (p-value=0.04).

Adverse events in ulcerative colitis patients on cannabinoids vs placebo

Irving et al. 2018 reported that AEs were more common in the Cannabinoid group. All the UC patients in the cannabinoid group suffered from AEs (29/29) compared to 77% (24/31) in the placebo group. There was no significant difference in the rate of serious adverse events across the two groups. About 10% of the participants in the cannabinoid had an SAE (worsening of disease, pregnancy complication), compared to 3% in the placebo group.

Dizziness, somnolence, dry mouth, vomiting, memory impairment, headache, lower respiratory tract infections, fatigue, and disorientation were some commonly reported AEs in the cannabinoid group. Study withdrawals were more frequent in the cannabidiol group (34%) compared to the placebo group (16%).

Only, Naftali et al. 2018[35], reported that no SAEs were observed without additional data. Naftali et al. 2021[33], reported an insignificant difference in the side effect profile of the two groups, and these side effects were minor and did not lead to treatment cessation.

Discussion

The pooled endoscopic disease activity did not appear to be significantly different across the two groups in this study. Although, the individual studies by Naftali et al. 2018[35] and Naftali et al. 2021[33], did report a significant difference in the endoscopic Mayo score of UC patients on cannabinoids compared to a placebo. It was also found that there was a non-significant difference in the CRP level; however, there was a significant difference in the Calprotectin levels reduction in the treatment group compared to the control group. It is possible that cannabinoids do not have much of an effect on disease activity parameters that relate to inflammation. Both Doeve et al. and Vinci et al. concluded similarly, reporting little to no impact of cannabinoids on remission or inflammatory biomarkers[29,30]. In contrast, recent studies in animal models of intestinal inflammation have shown a reduction in colonic inflammation, with degrading enzymes for endocannabinoids; such as fatty acid amide hydrolase inhibitors and cannabidiol[37,38]. Another recent study by Moniruzzaman et al. reported that the efficacy of cannabidiol could be increased by using protein nanoparticles to treat inflammatory bowel disease[39]. It is possible that changing the formulation of cannabinoids might confer adequate intestinal anti-inflammatory activity seen in humans compared to that witnessed only in animals.

However, this study did find a significant reduction in disease activity indices; such as DAI and Lichtiger scores, after cannabinoid administration over eight weeks. This reduction is possible as these indices are based on patient-reported outcomes and well-being. Cannabinoids have a well-recognized psychotropic effect mediated through the CB1 receptor in the central nervous system[40]. Cannabinoids also have a definite role in reducing colonic and gastric motility, as evidenced by a significant reduction in bowel movements and severity of abdominal pain in the intervention group: as seen in the current and previous RCTs and meta-analysis[41]. A reduction in visceral hyperalgesia due to TRPV1 downregulation contributes to symptom improvement as well[24].

This review found that cannabinoids led to a significant improvement in the QOL of patients. This is an important finding for patients with a quiescent disease or when in remission when in treatment modalities are limited. Cannabinoids can be important in this group of patients when they require only symptomatic relief. Reducing pain and bowel movements can be a welcome relief for UC patients. A recent analysis of the UK Medical cannabis registry reported a short-term improvement in IBD-specific symptoms and QOL of IBD patients. Prior cannabis consumers reported a more significant improvement compared to cannabis-naïve individuals[42]. Recent Cochrane reviews have also described the effect of cannabis in UC with almost similar findings[27–30].

Limitations

Clinical heterogeneity in the included studies, regarding the varied cannabinoid doses, formulations and outcome measures, is possibly this study's most significant limitation. Subgroup analyses were impossible because there was a limited number of studies and sample populations in this systematic review; additionally, the meta-analysis varied in regard to the disease activity indices used. Due to a standardized mean difference being used, this

makes it difficult to estimate the actual difference in disease activity scores. Also, the most recent included study by Metalon et al. seemed to be associated with a considerable risk of bias that might affect the pooled estimate. However, sensitivity analysis did not significantly affect the results, with the disease activity index remaining low in the intervention group.

As only RCTs were included and not non-randomized studies, only 2-3 studies could be included for each pooled result. The individual RCTs also had a limited sample size, and studies with small sample sizes and significant treatment effects might have skewed the results. Lack of matching, restriction and statistical adjustment of potential confounders in individual studies, such as baseline therapy, smoking status, disease stage, and degree of steroid resistance, might have further distorted the results. This lack of statistical adjustment was also present in the review process, as most studies failed to report complete data. Safety is as important a parameter as efficacy. However, incomplete data from individual studies made a comprehensive safety analysis beyond the scope of this study. Moreover, two of the studies were conducted by the same research group: Neftali et al.; and one study by Metalon et al. suffered from a significant risk of bias. A meta-regression analysis to investigate potential causes of heterogeneity would have given better results.

These limitations make it challenging to establish which patient subgroups, cannabis doses and formulations would be most efficacious.

What this study adds

This study analyzed cannabinoid effectiveness in UC, focusing on disease activity variation through RCTs offering the highest level of evidence. Little evidence of cannabinoid mediated improvement in the disease course and remission could be established from this study,

manifested with non-significant changes in endoscopic scores and inflammatory markers, especially CRP. However, cannabinoid supplementation has a definite role in the symptomatic control of bowel movements and abdominal pain severity in patients with UC. This might improve patient-reported outcome measures; especially in those with mild disease. They offer a valuable alternative to pain control medications, although further studies comparing traditional painkillers with cannabinoids should be planned. Studies with larger sample sizes and standardized designs, doses, formulations and outcome measures would provide valuable insight into this area. The safety and abuse potential of cannabinoids and cannabis-mediated interactions combined with standard therapies is an area that requires further evaluation. Oral cannabidiol should be preferred, as it does not depend on smoking habits and avoids THC-mediated psychoactive effects[43]. Newer formulations, lower doses and longer durations of therapy might be required to obtain desired efficacy.

Conclusion

Medicinal cannabinoids might have a role in treating specific symptoms of UC (pain, bowel movements, and QOL), with good efficacy and negligible toxicity. However, minimal impact can be expected on the disease course and inflammatory burden. Therefore, they can only serve as valuable adjuvants to standard therapy for UC patients, mainly to improve the QOL of patients with mild to moderate disease. However, further studies are required to assess the efficacy of different formulations, doses, routes and adverse effects of cannabidiol in varied patient populations.

Author's contribution statement

All authors contributed significantly in concept, design, data acquisition, data analysis, interpretation, and statistical analysis.

Conflict of interest

There are no conflicts of interest in connection with this article.

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