Real-world experience with Curcumin–QingDai combination for patients with active ulcerative colitis: A retrospective multicentre cohort study

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Summary

Background: Curcumin and QingDai (QD, Indigo) were shown effective for treating active ulcerative colitis (UC). We aimed to evaluate the real-world experience with the Curcumin–QingDai (CurQD) herbal combination to induce remission in active UC.

Methods: A retrospective multicentre adult cohort study from five tertiary academic centres (2018–2022). Active UC was defined as a Simple Clinical Colitis Activity Index (SCCAI) ≥ 3. Patients were induced by CurQD. The primary outcome was clinical remission at weeks 8–12, defined as SCCAI ≤ 2 and a decrease ≥ 3 points from baseline. Secondary outcomes: clinical response (SCCAI decrease ≥ 3 points), corticosteroid-free remission, faecal calprotectin (FC) response (reduction ≥ 50%), FC normalisation (FC ≤ 100 μg/g for patients with FC ≥ 300 μg/g at baseline) and safety. All outcomes were analysed for patients who were maintaining stable treatment.

Results: Eighty-eight patients were included; 50% were biologics/small molecules experienced, and 36.5% received ≥ 2 biologics/small molecules. Clinical remission...
was achieved by 41/88 (46.5%), and clinical response by 53/88 (60.2%). The median SCCAI decreased from 7 (IQR:5–9) to 2 (IQR:1–3), \( p < 0.0001 \). Of the 26 patients on corticosteroids at baseline, seven (26.9%) patients achieved corticosteroid-free remission. Among 43 biologics/small molecules experienced patients, clinical remission was achieved in 39.5% and clinical response by 58.1%. FC normalisation and response were achieved in 17/29 (58.6%) and 27/33 (81.8%) respectively. Median FC decreased from 1000\( \mu \)g/g (IQR:392–2772) at baseline to 75\( \mu \)g/g (IQR:12–136) at the end of inductions (\( n = 30 \) patients with paired samples), \( p < 0.0001 \). No overt safety signals emerged.

**Conclusion:** In this real-world cohort, CurQD effectively induced clinical and biomarker remission in patients with active UC, including the biologics/small molecules experienced patients.

1 | INTRODUCTION

Despite the recent advent of therapeutic agents for patients with active ulcerative colitis (UC), there is growing interest among patients and researchers in non-pharmaceutical options, such as dietary interventions and complementary medicine approaches, which are also among the topics most sought by patients on social media.\(^1\)\(^2\) Curcumin, an herbal traditional medicine compound, was shown by several placebo-controlled trials to be effective as an add-on therapy to 5-ASA in the induction and maintenance of remission in mildly-moderately active UC.\(^3\)\(^5\) Another plant-based compound, QingDai (QD, Indigo), was shown to ameliorate colitis in murine models and uncontrolled observations in UC patients, possibly through activation of the aryl-hydrocarbon receptor (AhR) pathway.\(^6\)\(^8\) Subsequently, QD was shown effective in two Japanese clinical trials of patients with active UC.\(^9\)\(^10\) We recently reported results of a randomised double-blinded placebo-controlled trial demonstrating that Curcumin and QD combination (CurQD) was superior to placebo in inducing remission in patients with active UC, many of whom were biologics experienced.\(^11\) In the present study, we aimed to report our real-world experience using this herbal combination in patients with active UC.

2 | MATERIALS AND METHODS

2.1 | Design and patients

This was a retrospective multicentre cohort study including patients with active UC cared for in five tertiary academic centres in Israel between March 2018 and January 2022 and correspondingly treated in a specialised Integrative Medicine clinic with CurQD to induce remission.

Eligible patients were ≥18 years old, had a known diagnosis of UC (by established clinical-endoscopic and histological criteria), and had active UC at the time of initiation of CurQD therapy, according to the treating physician. Patients starting CurQD therapy while in clinical remission were excluded. All participants had to be followed and cared for in parallel in one of the participating medical centres.

Disease activity was prospectively graded in the Integrative Medicine clinic using the Simple Clinical Colitis Activity Index (SCCAI),\(^12\)\(^-\)\(^14\) a validated scoring system widely used and based only on clinical symptoms. A SCCAI score of 0–2 was considered remission, a SCCAI score of 3–5 was considered mild colitis, a SCCAI score of 6–11 was moderate colitis and a SCCAI score >12 was severe colitis. Endoscopic activity (if available) was graded by the treating physicians based on the Mayo endoscopic score system.\(^15\)

CurQD was supplied by EviNature and manufactured at a GMP facility where it undergoes quality supervision according to Israeli regulatory standards (including routine testing for heavy metals, pesticides and microbial contaminants). CurQD was also tested by a third-party laboratory (Bar-Ilan University, Israel) for determining indigo and indirubin content (by LC–MS/MS analysis).\(^16\) The CurQD was administered in an Integrative Medicine clinic by a single licensed herbalist (N.S.) who followed these patients with the treating physicians. Patients received capsules of 500 mg of herbal extract dry powder daily. The capsules were comprised of varying doses ranging between 2 and 3 gr of ‘gut-directed’ Curcumin (free from any chemical excipient) and 0.5–2 gr of QD in combination. Dosage was elected according to clinical severity as assessed in real time by the experienced herbalist (N.S.), a case-by-case decision. The induction dose was 2 gr Curcumin +1 gr QD. A higher dose of 3 gr Curcumin +2 gr QD was used in moderate–severe cases (SCCAI scores >10), and a lower dose of 2 gr Curcumin +0.5 gr QD was used in milder cases (SCCAI 3–4). Patients were contacted routinely by the Integrative Medicine clinic at week 2 and the end of the induction period and were instructed to report if they experienced any adverse effects such as headaches, nausea, chest pain or shortness of breath. Follow-up was done by phone, email or text messaging, and in person or via online communication at the end of the induction.
Clinical and demographic data were extracted from patients’ charts in the participating medical centres and the Integrative Medicine clinic. We recorded biomarker levels (faecal calprotectin [FC]) at baseline if they were obtained up to 3 months from initiating the CurQD therapy and at the end of induction if performed within 1 month, and only if during those periods no change in medication(s) has occurred.

2.2 Outcomes and definitions

The primary outcome was the percentage of patients who achieved clinical remission defined as SCCAI ≤2 and a decrease of ≥3 points from baseline while maintaining stable treatment within the CurQD induction period (until weeks 8–12). Hospitalisation for UC exacerbation or any treatment escalation were considered treatment failure (even if patients continued the CurQD).

Secondary outcomes included: the percentage of patients with clinical response (a decrease in SCCAI of ≥3 points from baseline), corticosteroid-free remission in patients using corticosteroids at baseline, biomarker response and remission based on the change in FC levels throughout the induction period (FC response was calculated as a reduction of ≥50% in FC levels compared to baseline, FC remission was defined FC ≤100μg/g at the end of induction for patients with FC ≥300μg/g at baseline), endoscopic improvement (decrease ≥1 points in the Mayo endoscopic subscore) and endoscopic remission (Mayo endoscopic subscore 0); all outcomes only for patients who were maintaining stable treatment within the CurQD induction period.

2.3 Statistical analysis

Descriptive statistics were performed using medians and 25%–75% interquartile ranges (IQRs) for continuous variables and percentages for categorical variables. Wilcoxon paired test was used to compare pre–posttreatment variables. Analysis was performed using IBM SPSS statistics, version 28.0, IBM Corp. 2021, and graphics with Prism 9 for macOS Version 9.5.0, November 2022.

3 RESULTS

3.1 Patient population

Overall, 88 patients treated with CurQD for UC were included. Most patients had left-sided or extensive disease; nearly two-thirds had moderate–severe disease activity at the start of CurQD therapy (SCCAI >5). Half (50%) were biologics/small molecules experienced, and 84% were previously treated with corticosteroids, reflecting the mix of the UC population treated and cared for in the five participating academic medical centres. Thirty-seven patients (31.4%) received an add-on CurQD while continuing concomitant biologics/small molecules (all were nonresponders or partial responders to the biologics/small molecules). Except for one patient who started CurQD therapy 2 weeks after ustekinumab induction, all other patients were in their maintenance period of the respective concomitant biologic/small molecule at the time of CurQD therapy start. Demographics and baseline characteristics of the patient population are depicted in Table 1.

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<th>TABLE 1 Demographics and baseline characteristics.</th>
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<td>Median age, years (IQR)</td>
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<td>Median disease duration, years (IQR)</td>
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<td>Disease extent, n (%)</td>
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<td>Activity at baseline, n (%)</td>
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<td>Severe (SCCAI ≥12)</td>
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<td>Faecal calprotectin (FC) μg/g, median (IQR) available data for 45 patients</td>
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<td>Fc ≥300, n (%)</td>
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<td>Mayo endoscopic subscore (MES), n (%) available data for 42 patients</td>
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<td>Corticosteroids</td>
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<td>Biologics/small molecules</td>
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Abbreviations: 5-ASA, 5-aminosalicylic acid; 6-MP, 6-mercaptopurine; Mayo ES, Mayo endoscopic subscore; SCCAI, Simple Clinical Colitis Activity Index.

*aOut of patients with available data.

Most of the cohort, 60 patients (68.1%), were treated with an induction dose of 2gr Curcumin +1gr QD. A higher induction dose (3gr Curcumin + 2gr QD) was used in 15 patients (17%) who had moderate–severe disease based on SCCAI scores >10. Lower doses (2 gr Curcumin + 0.5 gr QD) were used in 13 patients (14.9%) with milder disease based on SCCAI scores between 3 and 4.

### 3.2 | Outcomes

During the CurQD induction period, only 73 of the 88 patients (83%) maintained stable therapy, four patients (4.5%) were hospitalised for UC exacerbations and required systemic corticosteroids, 10 patients (11.4%) had treatment escalation despite the continuation of CurQD (either 5-ASA add-ons or switched biologics/small molecules), and one patient (1.1%) started CurQD 2 weeks after ustekinumab and thus could not be considered for the CurQD efficacy analysis.

Overall, induction therapy with CurQD yielded clinical remission in 41/88 (46.5%) patients and clinical response in 53/88 (60.2%) patients (Figure 1). Among the entire cohort of 88 patients, the median SCCAI decreased from 7 (IQR 5–9) to 2 (IQR: 1–3) points, p < 0.0001; among the 73 patients who were on stable therapy through the induction period, the median SCCAI decreased from 6 (IQR 5–9) to 2 (IQR: 1–3) points, p < 0.0001 (Figure 2A).

Among patients with mild disease (SCCAI 3–5, n = 29), clinical remission and clinical response rates were similar, achieved in 13/29 (44.8%) patients. In the subgroup of patients with moderate–severe disease (SCCAI >5, n = 58), clinical remission was achieved in 28/58 (48.3%) patients and clinical response in 40/58 (69%). Among biologics/small molecules experienced patients (n = 43), the clinical remission rate was achieved in 17/43 (39.5%) patients and clinical response in 25/43 (58.1%) patients. A sensitivity analysis restricted to patients induced by CurQD without concomitant corticosteroids (n = 62) demonstrated that clinical remission and clinical response were achieved in 30/62 (48.4%) and 39/62 (62.9%) patients respectively. Of the 26 patients who were on corticosteroids at baseline, 13 (50%) were weaned off corticosteroids by the end of the induction period, and 7 (26.9%) achieved corticosteroid-free remission.

Twenty-seven of these 33 patients with paired FC levels (81.8%) had FC response at the end of the induction period (a decrease ≥50% of baseline value while maintaining stable therapy throughout induction), and 17/29 (58.6%) patients with a baseline FC ≥300 μg/g achieved FC remission (FC≤100 μg/g), see Figure 1. Thirty patients of these 33 patients with paired FC levels maintained stable therapy throughout induction; in this subgroup, the median of differences in FC levels was 605 μg/g (IQR:1906–276), corresponding to a 92.7% decline (IQR: 97.7%–80.3%) from baseline. Median FC decreased from 1000 μg/g (IQR: 392–2775) at baseline to 75 μg/g (IQR: 12–136) at the end of the induction period, p < 0.0001 (Figure 2B).

Data on paired FC among biologics/small molecules experienced patients were available for 15 patients only, revealing FC response in 13/15 (86.7%) and FC remission (relevant for patients who had FC ≥300 μg/g at baseline) in 7/12 (58.3%) patients.

Only 25 patients had endoscopic data at baseline, the majority (85%) with moderate–severe disease (Table 1). Of these, nine patients who maintained stable therapy throughout induction had an endoscopic assessment at baseline and the end of induction: 8/9 (88.8%) had endoscopic improvement (decrease ≥1 point in Mayo endoscopic subscore), and four patients achieved endoscopic remission (Mayo endoscopic subscore of 0).

### 3.3 | Safety

Four (4.5%) patients had modest (up to X3 times upper normal) liver transaminase enzyme elevations, which resolved in all either with the continuation of CurQD at the same dose or a 50% reduced dose. Two (2.3%) patients had self-limiting headaches upon the first few days of treatment. Four patients (4.5%) were hospitalised during treatment due to exacerbation of the disease, all considered treatment failures (this subgroup had an average SCCAI of 7.75 at the time of CurQD induction). Another patient with mild colitis completed the induction but did not respond and increased the SCCAI from 3 to 5 and then switched to a different strategy. No other adverse events were reported.

![Figure 1](image-url) Primary and secondary outcomes at the end of induction (weeks 8–12). Clinical response: a decrease in Simple Clinical Colitis Activity Index (SCCAI) ≥3 points from baseline; Clinical remission: SCCAI ≤2 and a decrease of ≥3 points from baseline. Biomarker response: reduction of ≥50% in faecal calprotectin (FC) levels compared to baseline; Biomarker remission: FC ≤100 μg/g at the end of induction, calculated for patients with FC ≥300 μg/g at baseline. For any response or remission, a patient must have maintained stable therapy throughout the CurQD induction period.

### 4 | DISCUSSION

A host of pharmaceutical agents has recently become available for the treatment of active UC, but there is still a subset of patients whose disease is not controlled by current strategies. Moreover, adverse events, costs and prolonged pre-authorisation procedures may limit some patients’ access to these novel therapies. When coupled with the growing understanding of the role of dietary exposure...
in disease pathogenesis and the preference of some patients to look for ‘natural remedies’, this creates an unmet need to explore additional strategies, specifically those based on dietary interventions and/or plant-based agents. Recently, in the present study, we follow-up on a previous short report from Israel and report a more comprehensive large multicentre real-world experience using an herbal combination of Curcumin and QingDai (CurQD) for the treatment of active UC. We showed that in a population of patients with moderate–severe UC, of whom half were experienced with biologics/small molecules, a short intervention with CurQD was effective and safe; clinical response was achieved in 60.2% of patients, and clinical remission in 46.5% of patients and there was also a significant improvement FC response (81.8%).

Curcumin is the active ingredient of Turmeric (the Rhizoma Curcuma Longa plant). Two meta-analyses of placebo-controlled trials and a systematic literature review concluded it has efficacy in inducing remission in mild–moderate UC. Similarly, two placebo-controlled trials from Japan found QD effective for inducing remission in active UC, including in patients who were resistant to biologics. These two herbal compounds have been available as a food supplement in Israel and have been given in combination since 2016 to patients with active UC. We have recently reported the results of an Israeli-Greek placebo-controlled trial showing the superiority of this combination over placebo to induce and maintain remission in patients with active UC, of whom many were biologic experienced. The present study supports the above observations in a real-world cohort of patients with UC treated in five tertiary academic centres, demonstrating that this herbal combination can induce clinical and biomarker remission in patients with moderate–severe active UC, of whom half were biologic experienced (Table 1, Figure 1). Interestingly, therapy outcomes did not differ much when limited to the subgroup of biologically experienced patients, suggesting that similar to reports with some of the newer small molecules, CurQD may exert its action independent of patients’ prior failure or experience with biologics.

CurQD treatment in this study was overall safe without any overt safety signals. It was previously reported in rare cases that QD was associated with reversible pulmonary arterial hypertension (PAH) when used in high doses for prolonged periods. In this cohort, no clinical cases of shortness of breath or other clinical signs of PAH were observed. However, it should be noted that we did not assess PAH with dedicated studies (since CurQD is considered a food supplement). Moreover, no such cases were observed in the clinical trial conducted with the same CurQD formulation. We acknowledge that short exposure and short follow-up period in these two studies and the fact that we did not actively test for PAH in this retrospective cohort may have masked this phenomenon. However, our experience with many patients using this combination long term did not reveal a single case of PAH. Whether the lack of PAH cases relates to the different sources of CurQD used in Israel or whether it is due to our protocol whereby CurQD is used for induction of remission followed by tapered QD dose within the combination to a predominantly Curcumin-based formulation for the maintenance phase is hitherto unknown. Headaches and liver enzyme elevations affected a minority of patients and were also previously reported in association with QD by others but are generally self-limiting or respond to dose reduction.

Finally, although Curcumin has been widely used for inflammatory bowel diseases and other medical conditions and is considered a safe supplement, there have been some reports on potential hepatotoxicity from Curcumin, mostly related to Turmeric. As aforementioned, Turmeric is the Curcuma Longa plant in which Curcumin is one of many compounds (believed to be the active one) along with compounds present in the form of volatile oil (mono and sesquiterpenoids) and others. This complexity of the compounds in Turmeric makes it difficult to attribute these Drug-Induced Liver Injuries (DILIs) specifically to the 95% purified Curcumin (as used in the present study) rather than to the other compounds within the non-purified whole Turmeric extract. Moreover, in some analyses, DILI events were suspected to be partly related to piperine excipients added to the extract to allow enhanced systemic absorption.

Notably, these excipients are deliberately not included in our patients’ Curcumin formulation, designed to reduce systemic absorption, and increase local mucosal exposure.

Limitations of our study mainly stem from its retrospective nature. Patients with missing critical data were excluded, as common to any real-world retrospective study. We could not assess the impact of
CurQD therapy on important components of disease activity like urgency and rectal bleeding as these data were not separately recorded, we do not have accurate data on the stability of concomitant therapies that were started before CurQD initiation, and we could not assess exposed patients who were lost to follow-up. All these variables might skew the actual real-world outcomes. Additionally, we herein report a short follow-up period, restricted to the induction period; however, we and others have reported extended successful experience with these herbal compounds,11,19,22 including in the paediatric population.30

Another limitation is the nonsystematic assessment of biomarkers, including missing data and inconsistent timing of testing, and the absence of repeated endoscopic assessments in most patients included. Notably, this reflects real-world practices and clinical indices, and documented biomarker responses support the validity of the observations.

In conclusion, this real-world multicentre experience suggests the efficacy and safety of CurQD monotherapy or as an add-on therapy (with other medications) for patients with active UC, including in biologics experienced patients, but more studies are warranted to further our knowledge about this herbal combination approach.

AUTHOR CONTRIBUTIONS
Henit Yanai: Conceptualization (lead); data curation (equal); formal analysis (lead); investigation (lead); methodology (lead); writing – original draft (lead); writing – review and editing (lead). Nir Salomon: Conceptualization (lead); data curation (lead); formal analysis (supporting); investigation (lead); project administration (lead); writing – review and editing (equal). Adi Lahat: Data curation (equal); writing – review and editing (equal). Bella Ungar: Data curation (equal); writing – review and editing (equal). Abraham Elakim: Data curation (equal); writing – review and editing (equal). Ofra Kriger-Sharabi: Data curation (equal); writing – review and editing (equal). Hilla Reiss-Mintz: Data curation (equal); writing – review and editing (equal). Benjamin Koslowsky: Data curation (equal); writing – review and editing (equal). Ariella Bar-Gil Shirit: Data curation (equal); writing – review and editing (equal). Natalie Tamir-Degabli: Data curation (equal); writing – review and editing (equal). Iris Dotan: Data curation (equal); writing – review and editing (equal). Nitsan Maharshak: Data curation (equal); writing – review and editing (equal). Ayal Hirsch: Data curation (equal); writing – review and editing (equal). Shomron Ben-Horin: Conceptualization (lead); data curation (equal); formal analysis (supporting); investigation (lead); methodology (lead); resources (lead); writing – original draft (supporting); writing – review and editing (equal). Uri Kopylov: Conceptualization (lead); data curation (equal); formal analysis (supporting); investigation (lead); methodology (lead); writing – original draft (supporting); writing – review and editing (equal).

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