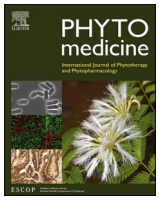
Phytomedicine 141 (2025) 156715

Contents lists available at ScienceDirect

Phytomedicine

journal homepage: www.elsevier.com/locate/phymed



Original Article

Add-on effect of curcumin to dienogest in patients with endometriosis: a randomized, double-blind, controlled trial

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ARTICLE INFO

Keywords:
Curcumin
Dienogest
Endometriosis
Pain
Quality of life

ABSTRACT

Background: Endometriosis is a chronic gynecological disorder characterized by significant pain and reduced quality of life (QOL). Current treatments, such as dienogest, are not fully effective, prompting the investigation of curcumin as a potential adjunct therapy. Although curcumin has demonstrated promise in preclinical studies, its clinical efficacy in endometriosis, particularly in combination with standard therapies like dienogest, remains underexplored.

Purpose: This is the first study aimed to evaluate the add-on effect of curcumin in combination with dienogest on pain relief, QOL, and sexual function in women with endometriosis.

Study Design: A randomized, double-blind, placebo-controlled trial was conducted to compare the efficacy of curcumin combined with dienogest versus dienogest alone with a placebo.

Methods: Eighty-six women aged 18–45 with stage 2–3 pelvic endometriosis and moderate to severe pain (visual analogue scale (VAS) ≥ 4) were randomly assigned in a 1:1 ratio to receive either nanocurcumin soft gel capsules (80 mg/day) or a placebo, along with dienogest (2 mg/day), for 8 weeks. Outcomes were assessed using adjusted mean differences (aMD) and 95 % confidence intervals (CIs).

Results: After 8 weeks, the curcumin and dienogest group demonstrated significantly greater improvements in pain scores compared to the placebo group: dysmenorrhea (aMD: −1.55, 95 %CI: −2.04 to −1.06; $p < 0.001$), dyspareunia (aMD: −0.93, 95 %CI: −1.37 to −0.49; $p < 0.001$), chronic pelvic pain (aMD: −1.55, 95 %CI: −2.04 to −1.06; $p < 0.001$), and dyschezia (aMD: −0.30, 95 %CI: −0.58 to −0.03; $p = 0.030$). Additional benefits were observed in QOL and Female Sexual Function Index (FSFI) scores, except for the orgasm domain. Differences in endometrioma size were not statistically significant.

Conclusion: The combination of curcumin and dienogest significantly reduced pain and improved QOL and sexual function in women with endometriosis, suggesting curcumin as an effective adjunct therapy.

Abbreviations

VAS	visual analogue scale
aMD	adjusted mean difference
QOL	quality of life
FSFI	Female Sexual Function Index
PGs	prostaglandins
IRCT	Iranian registry of clinical trial
CONSORT	CONsolidated Standards of Reporting Trials
rAFS	American Society for Reproductive Medicine classification
OCP	Oral Contraceptive Pills
WHO	World Health Organization
SD	standard deviation
BMI	body mass index

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https://doi.org/10.1016/j.phymed.2025.156715
Received 7 December 2024; Received in revised form 18 March 2025; Accepted 31 March 2025
Available online 1 April 2025

Introduction

Endometriosis is a chronic gynecological disorder characterized by the presence of endometrial-like tissue outside the uterine cavity, commonly affecting women of reproductive age (Bulun et al., 2019). It is a prevalent condition, with estimates suggesting that approximately 10 % to 15 % of women worldwide are affected (Della Corte et al., 2020).

Although not all women with endometriosis exhibit symptoms, the disease is often associated with pelvic pain and infertility, significantly impacting not only the individuals affected but also their partners and families. Endometriosis, particularly its associated pain, has been found to significantly impair quality of life (QOL), affecting various aspects such as physical ability, daily routines, social interactions, educational and professional pursuits, sexual relationships, and mental and emotional well-being (Missmer et al., 2021; Smolarz et al., 2021).

National and international guidelines unanimously recommend combined oral contraceptive pills and progestogens as first-line therapies for endometriosis-associated pain. However, discrepancies exist regarding recommendations for second- and third-line treatments (Kalaitzopoulos et al., 2021). When progestins and estroprogestins prove ineffective, gonadotropin-releasing hormone (GnRH) analogs are typically prescribed as the next line of treatment (Christian et al., 2022). Nevertheless, significant adverse effects associated with GnRH analogs necessitate the use of add-back therapy and limit their overall effectiveness. Notably, nearly 15 % of patients experience no improvement in pain, while pain persists in 5 % to 59 % of cases even after treatment completion (Becker et al., 2017).

Dienogest, a synthetic progestin, is widely used as a monotherapy for endometriosis due to its ability to reduce endometriotic lesion size and alleviate endometriosis-associated pain. However, its effectiveness remains suboptimal for some patients, with reports indicating that a proportion of individuals experience persistent or recurrent pain despite treatment. Additionally, while dienogest effectively reduces pain, it has been associated with hypoestrogenic side effects, such as decreased bone mineral density, vaginal dryness, mood changes, and breakthrough bleeding, which may impact long-term adherence (Li et al., 2024). These limitations highlight the need for alternative or adjunct therapies that can enhance treatment efficacy, improve patient adherence, and minimize adverse effects (Garzon et al., 2021).

Oxidative stress plays a critical role in stimulating the production of inflammatory mediators, such as cytokines, reactive oxygen species, and prostaglandins (PGs), within endometriotic implants. This discovery has prompted extensive research into a wide range of antioxidants through both preclinical and clinical trials (Baboo et al., 2019; Clower et al., 2022; Santanam et al., 2013).

Curcumin, a bioactive compound derived from the rhizome of *Curcuma longa*, has garnered attention for its potential therapeutic benefits in various inflammatory conditions, including endometriosis. Preclinical studies have demonstrated its anti-inflammatory, anti-angiogenic, and anti-fibrotic properties, suggesting a potential role in managing endometriosis-associated symptoms (Arablou and Kolahdouz-Mohammadi, 2018; Vallée and Lecarpentier, 2020).

Integrating curcumin into the treatment protocol alongside dienogest for endometriosis presents several compelling advantages. Curcumin exhibits potent anti-inflammatory and antioxidant properties, which can effectively target the inflammatory processes underlying endometriosis. Additionally, curcumin has been shown to modulate various signaling pathways involved in endometriosis pathogenesis, including those related to cell proliferation and apoptosis (Chowdhury et al., 2019; Ding et al., 2022). Therefore, combining curcumin with dienogest could offer a synergistic effect, inhibiting the growth of endometriotic lesions and promoting their regression. Furthermore, curcumin is generally well-tolerated and associated with minimal side effects, making it a safe adjunct therapy to complement dienogest. Given these potential benefits, our study aimed to evaluate the add-on effect of curcumin in combination with dienogest on pain relief, QOL, and sexual function in women with endometriosis.

Methods

Study design

This study was designed as an add-on, double-blind, randomized, placebo-controlled trial to compare the effects of dienogest plus curcumin versus dienogest plus placebo in patients with endometriosis. The trial was conducted at Ali Ibn Abi Talib Hospital, a university-affiliated hospital under Zahedan University of Medical Sciences. A total of 86 eligible patients were recruited and randomized in a 1:1 ratio to receive either nanocurcumin soft gel capsules (80 mg/day) or matching placebo, along with dienogest (2 mg/day), for a duration of 8 weeks.

Randomization and allocation concealment

To ensure proper randomization and minimize selection bias, a block randomization method with variable block sizes ranging from 2 to 6 was employed. The randomization sequence was generated using a computerized random number generator (www.sealedenvelope.com). To maintain strict allocation concealment, the generated sequence was implemented using sequentially numbered, sealed, opaque envelopes.

An independent epidemiologist, who was not involved in patient recruitment, clinical assessments, or data analysis, was responsible for conducting the random allocation process and maintaining secure allocation concealment throughout the study. The allocation details were coded and kept strictly confidential until the trial was completed. This ensured that no investigator, clinician, or participant could predict the treatment assignment, thereby preventing selection bias.

Blinding process

To eliminate potential bias and enhance the internal validity of the study, a double-blind design was implemented, ensuring that multiple stakeholders remained unaware of treatment allocation. Specifically, the following individuals were blinded throughout the study: Participants were blinded to their assigned intervention, as both curcumin and placebo capsules were identical in shape, size, color, texture, and odor. This prevented any potential bias related to treatment perception. The healthcare professionals responsible for patient care, symptom management, and follow-up evaluations remained unaware of the treatment allocation, ensuring that medical decisions were not influenced by the assigned intervention. To prevent detection bias, all personnel involved in outcome assessments, data collection, and statistical analyses were blinded to group assignments. This measure ensured that subjective assessments and data interpretation remained unbiased.

This trial was approved by the institutional review board and the ethics committee of Zahedan University of Medical Sciences, (approval ID: IR.ZAUMS.REC.1401.285 and approval date: 2022-10-25) and was registered in the Iranian registry of clinical trial (IRCT) under registration number is IRCT20221111056469N1 and the trial registration date was (2022-11-16). All participants provided written informed consent before enrollment in the study. They were informed about the study's objectives, procedures, potential risks, and benefits, as well as the publication of anonymized data in a scientific journal. The trial was conducted in accordance with Good Clinical Practice guidelines and reported in accordance the CONSORT (CONsolidated Standards of Reporting Trials) 2010 guideline.

Study participants

Women aged 18–45 years with endometriosis who were referred to the hospital were invited to participate in the study based on the following inclusion criteria: 1) Laparoscopic diagnosis of pelvic endometriosis with related symptoms, such as dysmenorrhea, dyspareunia,

dyschezia, and chronic pelvic pain, 2) having moderate to severe endometriosis-associated pain (VAS≥ 4) and, 3) Stage II or III endometriosis according to the revised American Society for Reproductive Medicine classification (rASRM). The exclusion criteria were 1) use of gonadotropin-releasing hormone agonists (in the last 6 months), progestins, dienogest or danazol (in the last 3 months), or other oral contraceptive pills (OCPs) OCPs (in the last 1 month), 2) gynecological malignancy, 3) other gynecological disease in conjunction with endometriosis identified by ultrasound or MRI (e.g. non-endometrioid ovarian cyst, fibroids), 4) underlying diseases such as a cardiovascular, respiratory, renal, hematologic, hepatic, neurologic, or psychological conditions and, 5) no contraindications to curcumin or dienogest.

Intervention

All women were treated with oral dienogest (Visanne, Bayer Pharma AG, Germany) at a dosage of 2 mg per day, starting on days 2–5 of menstruation and continuing without interruption for 8 weeks. To enhance the bioavailability of curcumin, we utilized SinaCurcumin oral capsules (Exir Nano, Tehran, Iran) for our research. SinaCurcumin is a nanomicellar formulation of curcumin approved by the Food and Drug Administration in Iran (IRC: 1228225765) (Hassaniazad et al., 2021). Curcuminoids, the active components of curcumin, are natural polyphenolic compounds derived from the dried roots of Curcuma longa l. (turmeric). The curcuminoid complex consists of curcumin (approximately 77 %), desmethoxycurcumin (approximately 17 %), and bisdemethoxycurcumin (approximately 6 %), collectively referred to as the C3 complex. Each soft gelatin capsule of SinaCurcumin contains 80 mg of curcuminoids formulated as nanomicelles, with a purity of >95 %. Micelles are spherical vesicles composed of surfactant molecules with amphiphilic properties that assemble spontaneously in water. They are commonly used to deliver poorly water-soluble drugs, such as curcumin. The curcumin-encapsulated polymeric micelles in SinaCurcumin were synthesized using a solid dispersion technique in a one-step process. These micelles have an average diameter of approximately 10 nm, as determined by dynamic light scattering, and exhibit nearly 100 % encapsulation efficiency. The small size of the micelles enhances cellular uptake and bioavailability, making them more effective than unformulated curcumin. Preclinical studies have demonstrated that the oral absorption of SinaCurcumin is at least 50 times greater than that of conventional curcumin powder, owing to its enhanced bioavailability. Furthermore, the stability of the curcuminoid content and the size distribution of nanomicelles remain consistent for at least 24 months (Hafez Ghoran et al., 2022).

Endpoints and clinical investigations

The primary outcome of interest in the study was the variation in pain levels reported by the patients. Pain intensity was measured using the Visual Analog Scale (VAS), a validated subjective tool for assessing acute and chronic pain. The VAS scores were recorded by having patients make a handwritten mark on a 10-cm line, representing a continuum between “no pain” and “worst pain” (Heller et al., 2016). Using this instrument, we measured pain associated with dysmenorrhoea, dyspareunia, dyschezia, dysuria, low back pain, sciatica and chronic pelvic pain. Secondary endpoints included changes in quality of life (QOL), assessed using the World Health Organization (WHO) QOL-BREF QOL questionnaire, sexual function, evaluated using the Female Sexual Function Index (FSFI) questionnaire; and the size of endometrioma, measured via transvaginal ultrasonography (5 MHz probe Fokuda, Japan) from baseline to week eight. The WHOQOL-BREF, developed by the WHOQOL Group, consists of 26 questions and evaluates overall QOL and general health across four domains: physical, psychological, social relationships, and environmental. Responses are recorded on a 5-point scale, with scores ranging from 0 ("The worst health you can imagine") to 100 ("The best health you can imagine") (Mehdizadeh Kashi et al., 2018). The FSFI is a validated instrument with 19-item self-administered items that addresses different aspects of sexual function. Responses are recorded on a 5-point scale, with total scores ranging from 2 ("The worst sexual function") to 36 ("The best sexual function") (Rosen et al., 2000).

Sample size

A total sample size of 86 women (43 per group), including a 15 % dropout rate, was calculated to provide 80 % power to detect a difference of two points in the mean VAS scores between the groups. This calculation assumed mean scores of five in the intervention group (dienogest plus curcumin) and seven in the control group (dienogest plus placebo), with a common standard deviation (SD) of three in both groups. A two-sided test with a type I error of 0.05 was used for this analysis.

Statistical analysis

All statistical analyses were conducted using Stata 17 (Stata Corp, College Station, TX, USA), based on the intention-to-treat approach, with a two-sided test and a type I error of 0.05. Continuous variables were described using mean ± SD, while categorical variables were summarized as counts (percentages). Baseline characteristics were compared between the two intervention groups using an independent sample *t*-test for continuous data and a chi-square test for categorical data. A multivariable mixed-effects linear regression model was employed to evaluate the adjusted mean difference (aMD) in the outcomes of interest between the two groups. The effect size was reported as aMD along with its 95 % confidence interval.

Results

Screening and recruitment

We recruited study participants over a 15-month period between November 2022 and March 2024. A total of 126 women were screened for eligibility, of whom 86 met the inclusion criteria and were enrolled in the study (43 patients in each group). Forty women were excluded, with the most common reason being failure to meet the protocol-specified VAS scores for dysmenorrhea, dyspareunia, or non-menstrual pelvic pain (27 patients). One patient in the intervention group migrated during the second month of follow-up and was excluded from the analysis. The participant flow diagram is shown in Fig. 1.

Baseline characteristics

Table 1 summarizes the baseline characteristics and clinical features of the study population. The mean ± SD age in the intervention and control groups was 33.81 ± 6.49 and 34.11 ± 6.44 years, respectively (mean difference [MD]: −0.30, 95 % confidence interval [CI]: −3.07, 2.47; $p = 0.829$). The mean ± SD body mass index (BMI) in the intervention group (dienogest plus curcumin) and the control group (dienogest plus placebo) was 23.98 ± 2.63 and 24.43 ± 3.38, respectively (MD: −0.44, 95 % CI: −1.75, 0.85; $p = 0.495$). Most patients in both groups were classified as stage III based on the revised American Society for Reproductive Medicine (r-ASRM) guidelines (62.79 % of the intervention group [$n = 27$] and 53.49 % of the control group [$n = 23$]; $p = 0.389$). The trial groups were comparable in terms of all demographic and clinical characteristics at baseline.

Principal findings

Table 2 presents the baseline, post-intervention, and change values for pain measurements in both groups. No significant differences were observed in the intended outcomes between the groups at baseline.

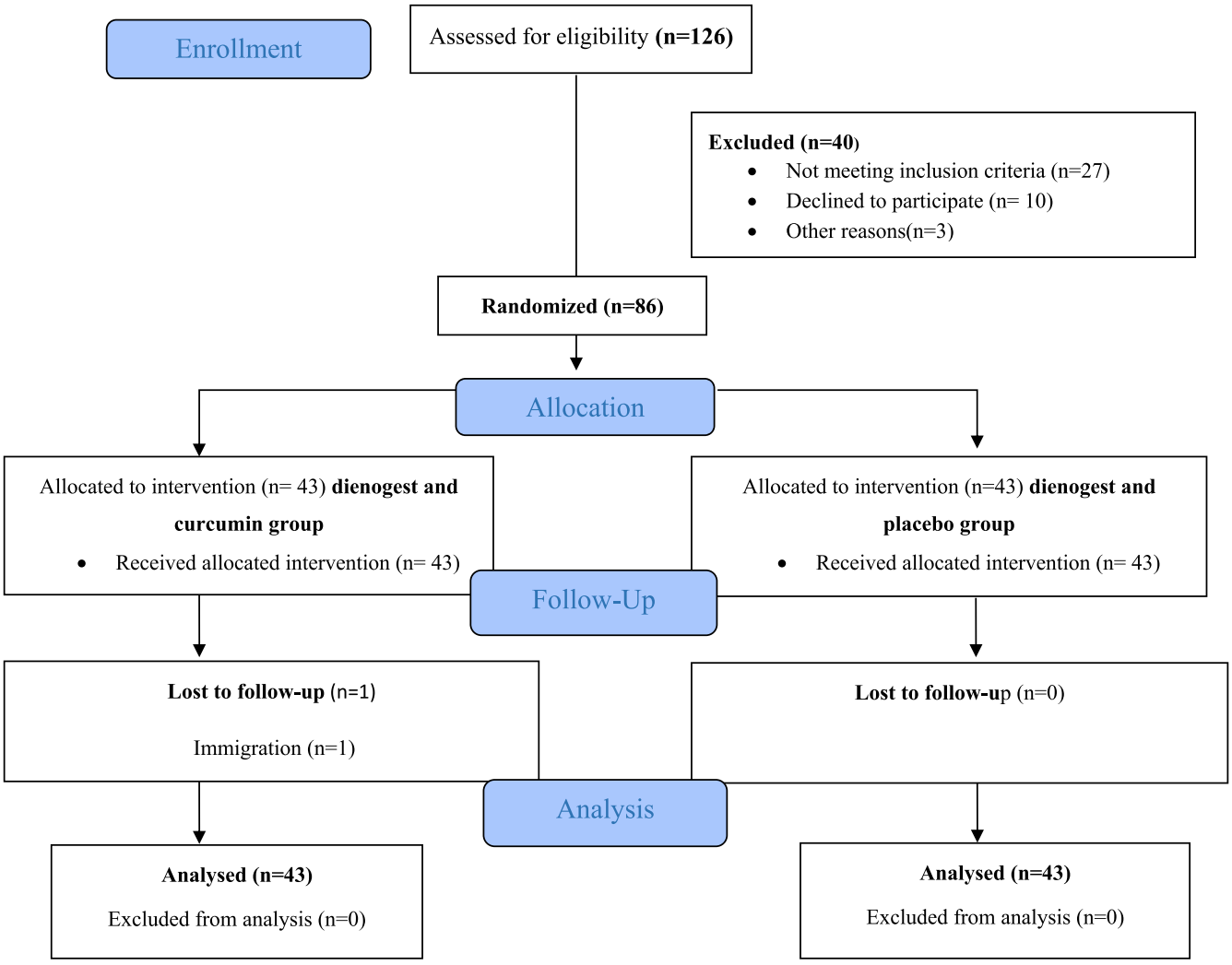

Fig. 1. Disposition of patients in a randomized, double-blind, controlled trial comparing the add-on effect of curcumin to dienogest for the treatment of endometriosis. Detailed reasons of withdrawal from the study are given: [a] selected other treatment; personal reason.

Dysmenorrhea decreased significantly more in the intervention group (dienogest plus curcumin), with VAS scores decreasing from 6.67 ± 1.20 to 2.07 ± 1.23 (a 68.96 % reduction), compared to the control group (dienogest plus placebo), where VAS scores decreased from 6.41 ± 1.02 to 3.44 ± 1.16 (a 46.33 % reduction) (change difference: −1.59, 95 % CI: −2.12, −1.08; $p < 0.001$). After adjusting for baseline VAS dysmenorrhea scores, BMI, age, analgesic usage, and endometriosis stage, the combination of dienogest and curcumin was associated with a significant improvement in dysmenorrhea compared to dienogest plus placebo (adjusted mean difference [aMD]: −1.55, 95 % CI: −2.04, −1.06; $p < 0.001$) (Table 2).

VAS dyspareunia scores also decreased significantly in the intervention group, from 4.83 ± 1.78 to 1.52 ± 1.34 (a 68.53 % reduction), compared to the control group, where scores decreased from 4.72 ± 1.65 to 2.39 ± 1.23 (a 50.84 % reduction) (change difference: −0.98, 95 % CI: −1.59, −0.37; $p = 0.002$). After adjusting for baseline VAS dyspareunia scores, BMI, age, analgesic usage, and endometriosis stage, the combination of dienogest and curcumin was associated with a significant improvement in dyspareunia compared to dienogest plus placebo (aMD: −0.93, 95 % CI: −1.37, −0.49; $p < 0.001$) (Table 2).

Total chronic pelvic pain scores decreased significantly in both groups by the end of treatment. However, the reduction was greater in the intervention group (VAS scores decreased from 6.37 ± 1.60 to 1.88 ± 1.38, a 70.48 % reduction) compared to the control group (VAS scores decreased from 6.09 ± 1.12 to 3.32 ± 1.26, a 45.48 % reduction) (change difference: −1.68, 95 % CI: −2.28, −1.08; $p < 0.001$). After adjustment for baseline chronic pelvic pain scores, BMI, age, analgesic usage, and endometriosis stage, the combination of dienogest and curcumin was associated with a significant improvement in chronic pelvic pain compared to dienogest plus placebo (aMD: −1.55, 95 % CI: −2.04, −1.06; $p < 0.001$) (Table 2).

A reduction in dyschezia was observed in the intervention group (VAS scores decreased from 6.04 ± 1.54 to 1.80 ± 1.50, a 70.19 % reduction) and the control group (VAS scores decreased from 5.83 ± 1.17 to 3.01 ± 1.38, a 71.73 % reduction) (change difference: −1.35, 95 % CI: −1.99, −0.70; $p < 0.001$). However, the multivariable model showed a significant difference between the two groups in dyschezia (aMD: −0.30, 95 % CI: −0.58, −0.03; $p = 0.030$) (Table 2).

For low back pain, a reduction was observed in the intervention group (VAS scores decreased from 6.09 ± 1.12 to 3.32 ± 1.26, a 45.48 % reduction) compared to the control group (VAS scores decreased from 6.09 ± 1.12 to 3.32 ± 1.26, a 48.37 % reduction) (change difference: −1.35, 95 % CI: −1.99, −0.70; $p < 0.001$). After adjustment for baseline low back pain scores, BMI, age, analgesic usage, and endometriosis stage, the combination of dienogest and curcumin was associated with a significant improvement in low back pain compared to dienogest plus placebo (aMD: −0.96, 95 % CI: −1.46, −0.46; $p < 0.001$) (Table 2).

Over the 8-week follow-up period, the combination of dienogest and

Table 1
Background and clinical features of two groups.

	Dienogest plus curcumin ($n = 43$)	Dienogest ($n = 43$)	p *
Age (year) [a]	33.81± 6.49	34.11± 6.44	0.829
Height (cm) [a]	166.09± 6.27	167.74± 5.57	0.200
Weight (kg) [a]	66.27± 8.87	68.95± 11.10	0.221
BMI (kg/m^2) [a]	23.98± 2.63	24.43± 3.38	0.495
Smoking [b]	18 (41.86)	15 (34.88)	0.506
r-ASRM stage of endometriosis (% women) [b]			
Stage II	16 (37.21)	20 (46.51)	0.389
Stage III	27 (62.79)	23 (53.49)	
Irregular menstruation [b]			
Regular	2 (4.65)	1 (2.33)	0.500
Irregular	41 (95.35)	42 (97.67)	
History of infertility [b]	18 (41.86)	15 (34.88)	0.506
Parity [b]			
Nulliparous	25 (58.13)	21 (48.83)	0.387
Multiparous	18 (41.87)	22 (51.17)	
History of miscarriage [b]	6 (13.95)	7 (16.27)	0.506

BMI: body mass index; r-ASRM: revised American Society for Reproductive Medicine.
[a] Values given as mean ± SD (standard deviation).
[b] Values given as number (percentage).
* Continuous variables compared with independent *t*-test, categorical variables compared with chi-square test or Fisher exact test.

curcumin was associated with a significant improvement in sciatica pain (VAS scores decreased from 5.37 ± 1.77 to 1.69 ± 1.43, a 68.52 % reduction) compared to the control group (VAS scores decreased from 5.30 ± 1.65 to 2.67 ± 1.42, a 49.62 % reduction) (change difference: −0.99, 95 % CI: −1.65, −0.33; $p = 0.004$). After adjustment for baseline sciatica pain scores, BMI, age, analgesic usage, and endometriosis stage, the combination of dienogest and curcumin was associated with a significant improvement in sciatica pain compared to dienogest plus placebo (aMD: −1.24, 95 % CI: −1.79, −0.69; $p < 0.001$) (Table 2).

Women in the intervention group (dienogest plus curcumin) had significantly lower total quality of life (QOL) scores (reflecting improvement) compared to the control group (dienogest plus placebo) at the end of follow-up (aMD: −11.29, 95 % CI: −16.05, −6.53; $p < 0.001$) (Table 3). The intervention group showed improvements in all QOL domains compared to the control group, with the greatest differences observed in the pain and self-image domains (Table 4).

The overall sexual function scores, assessed using the Female Sexual Function Index (FSFI), increased significantly in both groups by the end of treatment. However, the increase was significantly greater in the intervention group (scores increased from 21.10 ± 4.79 to 30.08 ± 5.13, a 42.55 % increase) compared to the control group (scores increased from 22.41 ± 4.11 to 26.81 ± 2.96, a 19.63 % increase) (change difference: 4.42, 95 % CI: 2.46, 6.37; $p < 0.001$) (aMD: 3.76, 95 % CI: 2.08, 5.45; $p < 0.001$) (Table 3). Scores in all domains except orgasm were higher in the intervention group compared to the control group (Table 5).

Results from the multivariate model showed a significant difference between the two groups in the size of the left endometrioma (aMD: −2.79, 95 % CI: −5.45, −0.13; $p = 0.040$) but no significant difference in the size of the right endometrioma (aMD: −2.90, 95 % CI: −8.10, 2.28; $p = 0.273$) at the end of the study, after adjusting for baseline endometrioma size, BMI, age, analgesic usage, and endometriosis stage (Table 2). Although the difference in the size of the right endometrioma was not statistically significant, it was also clinically non-significant.

Discussion

Main findings

In the present randomized clinical trial in women with endometriosis, we demonstrated, for the first time that 80 mg of curcuminoids formulated as nanomicelles add-on therapy with dienogest have high efficacy and safety for improving pain, sexual function and QOL. We observed statistical and clinical significant improvements in self-reported pain, including dysmenorrhea, dyspareunia, chronic pelvic pain, dyschezia, low back pain, and sciatica, after just 8 weeks of

Table 2
Mean (95 %CI) pain scores at base and post-treatment in dienogest plus curcumin and dienogest.

		Dienogest plus curcumin ($n = 42$) [€]	Dienogest ($n = 43$)		95 % CI		p
		Mean ± SD	**Mean ± SD**	Diff [#]	**Lower**	**Upper**	
Dysmenorrhea	Pre	6.67 ± 1.20	6.41 ± 1.02	0.25	−0.22	0.73	0.294[†]
	Post	2.07 ± 1.23	3.44 ± 1.16	−1.49	−1.95	−1.04	<0.001[§]
	Change	−4.57 ± 1.34	−2.97 ± 1.49	−1.59	−2.12	−1.06	<0.001
Dyspareunia	Pre	4.83 ± 1.78	4.72 ± 1.65	0.11	−0.62	0.85	0.755[†]
	Post	1.52 ± 1.34	2.39 ± 1.23	−0.93	−1.37	−0.49	<0.001[§]
	Change	−3.30 ± 1.50	−2.32 ± 1.30	−0.98	−1.59	−0.37	0.002
Chronic pelvic pain	Pre	6.37 ± 1.60	6.09 ± 1.12	0.27	−0.31	0.87	0.354[†]
	Post	1.88 ± 1.38	3.32 ± 1.26	−1.55	−2.04	−1.06	<0.001[§]
	Change	−4.45 ± 1.69	−2.76 ± 0.97	−1.68	−2.28	−1.08	<0.001
Dyschezia	Pre	2.30 ± 0.96	2.37 ± 1.06	−0.06	−0.5	0.36	0.752[†]
	Post	0.30 ± 0.71	0.67 ± 0.89	−0.3	−0.58	−0.03	0.030[§]
	Change	−0.97 ± 0.86	−1.69 ± 0.91	−0.27	−0.66	0.1	0.154
Dysuria	Pre	2.25 ± 0.92	2.34 ± 1.06	−0.09	−0.52	0.33	0.667[†]
	Post	0.30 ± 0.71	0.60 ± 0.87	−0.22	−0.49	0.04	0.109[§]
	Change	−1.92 ± 0.80	−1.74 ± 0.90	−0.18	−0.55	0.18	0.324
Low back pain	Pre	6.04 ± 1.54	5.83 ± 1.17	0.21	−0.37	0.79	0.481[†]
	Post	1.80 ± 1.50	3.01 ± 1.38	−1.24	−1.79	−0.69	<0.001[§]
	Change	−4.19 ± 1.77	−2.83 ± 1.17	−1.35	−1.99	−0.7	<0.001
Sciatica	Pre	5.37 ± 1.77	5.30 ± 1.65	0.06	−0.66	0.8	0.851[†]
	Post	1.69 ± 1.43	2.67 ± 1.42	−0.96	−1.46	−0.46	<0.001[§]
	Change	−3.61 ± 1.78	−2.62 ± 1.21	−0.99	−1.65	−0.33	0.004

[€] The missing value (one women in Dienogest plus curcumin group).
[#] Intervention minus control group.
[†] Based on *t*-test.
[§] Based on Linear Mixed-effects model (the included variables were: basic value of dependent variable, treatment type, BMI, age, analgesic usage and stage of endometriosis).

Table 3
Mean (95 %CI) scores of sexual function, quality of life and size of the endometrioma at base and post-treatment in dienogest plus curcumin and dienogest.

		Dienogest plus curcumin ($n = 42$) [€]	Dienogest ($n = 43$)		95 % CI		p
		Mean ± SD	**Mean ± SD**	Diff [#]	**Lower**	**Upper**	
FSFI	Pre	21.10 ± 4.79	22.41 ± 4.11	−1.31	−3.22	0.6	0.178[†]
	Post	30.08 ± 5.13	26.81 ± 2.96	3.76	2.08	5.45	<0.001[§]
	Change	8.81 ± 5.17	4.39 ± 3.78	4.42	2.46	6.37	<0.001
QOL	Pre	53.55 ± 17.03	51.75 ± 11.96	1.8	−4.51	8.11	0.572[†]
	Post	25.21 ± 13.60	36.03 ± 12.44	−11.29	−16.05	−6.53	<0.001[§]
	Change	−27.76 ± 15.44	−15.72 ± 11.46	−12.04	−17.92	−6.15	<0.001
Size of the endometrioma (Left)	Pre	23.37 ± 13.12	30.31 ± 12.62	5.76	0.2	11.32	0.042[†]
	Post	10.90 ± 9.50	10.34 ± 9.88	−2.79	−5.45	−0.13	0.040[§]
	Change	−12.76 ± 10.23	−7.25 ± 6.95	−5.50	−9.27	−1.73	0.005
Size of the endometrioma (Right)	Pre	24.30 ± 17.55	18.04 ± 13.92	6.26	−0.56	13.09	0.072[†]
	Post	11.66 ± 16.99	11.74 ± 9.77	−2.9	−8.1	2.28	0.273[§]
	Change	−12.64 ± 20.10	−6.30 ± 6.21	−6.34	−12.72	0.04	0.052

FSFI: female sexual function index, QOL: quality of life.
[€] The missing value (one women in Dienogest plus curcumin group).
[#] Intervention minus control group.
[†] Based on *t*-test.
[§] Based on Linear Mixed-effects model (the included variables were: basic value of dependent variable, treatment type, BMI, age, analgesic usage and stage of endometriosis).

Table 4
Mean (95 %CI) of quality of life domain scores at base and post-treatment in dienogest plus curcumin and dienogest.

		Dienogest plus curcumin ($n = 42$) [€]	Dienogest ($n = 43$)		95 % CI		p
EHP-30 domain scores		**Mean ± SD**	**Mean ± SD**	Diff [#]	**Lower**	**Upper**	
Pain	Pre	54.75 ± 17.65	55.28 ± 16.32	−0.52	−7.82	6.76	0.886[†]
	Post	18.93 ± 15.56	31.60 ± 15.68	−11.69	−17.37	−6.01	<0.001[§]
	Change	−35.33 ± 17.86	−23.67 ± 12.95	−11.65	−18.37	−4.93	0.001
Control and powerlessness	Pre	52.51 ± 16.71	51.74 ± 12.44	0.77	−5.54	7.09	0.808[†]
	Post	26.98 ± 16.28	37.01 ± 13.15	−10.19	−15.88	−4.51	<0.001[§]
	Change	−25.49 ± 17.84	−14.72 ± 13.94	−10.76	−17.66	−3.86	0.003
Emotional well-being	Pre	57.07 ± 33.42	49.90 ± 12.44	7.17	−3.64	17.98	0.191[†]
	Post	26.82 ± 14.01	37.50 ± 14.14	−10.96	−16.73	−5.19	<0.001[§]
	Change	−29.97 ± 36.02	−12.40 ± 16.25	−17.57	−29.89	−5.53	<0.001
Social support	Pre	52.47 ± 15.55	51.45 ± 12.92	1.01	−5.11	7.15	0.742[†]
	Post	26.93 ± 14.77	36.04 ± 13.49	−9.58	−14.69	−4.47	<0.001[§]
	Change	−25.59 ± 12.17	−15.40 ± 14.96	−10.18	−16.08	−4.29	0.001
Self-image	Pre	50.96 ± 16.48	50.38 ± 12.59	0.58	−5.71	6.87	0.855[†]
	Post	26.98 ± 14.47	37.98 ± 16.59	−11.03	−16.64	5.42	<0.001[§]
	Change	−24.01 ± 14.04	−12.40 ± 14.59	−11.60	−17.78	−5.42	<0.001
Sexual intercourse	Pre	6.04 ± 1.54	5.83 ± 1.17	0.21	−0.37	0.79	0.481[†]
	Post	1.80 ± 1.50	3.01 ± 1.38	−1.24	−1.79	−0.69	<0.001[§]
	Change	−4.19 ± 1.77	−2.83 ± 1.17	−1.35	−1.99	−0.7	<0.001

EHP: Endometriosis Health Profile.
[€] The missing value (one women in Dienogest plus curcumin group).
[#] Intervention minus control group.
[†] Based on *t*-test.
[§] Based on Linear Mixed-effects model (the included variables were: basic value of dependent variable, treatment type, BMI, age, analgesic usage and stage of endometriosis).

treatment with the combination therapy. The findings highlight the potential of curcumin as an adjunctive therapy to dienogest in alleviating various types of pain associated with endometriosis. This suggests a multifaceted approach to managing the complex and diverse symptoms experienced by patients with this condition. The improvements observed in QOL and sexual function are particularly noteworthy, as they reflect the broader impact of endometriosis on patients' overall well-being and intimate relationships.

Notably, the enhancements in QOL and sexual function were observed across all domains except orgasm. While the reasons for this discrepancy warrant further investigation, it is important to acknowledge that sexual dysfunction is a common and complex issue in women with endometriosis that may not be fully addressed by pharmacological interventions alone.

The significant improvements in pain, QOL, and sexual function observed in the intervention group underscore the potential clinical utility of combining curcumin with dienogest in the management of endometriosis. This may offer patients a more effective and well-rounded treatment approach compared to dienogest alone.

Interpretation

This study is the first to investigate the synergistic effects of curcumin and dienogest in endometriosis, addressing a critical gap in the literature. While previous studies have explored curcumin as a standalone therapy, our use of a nanomicellar formulation (SinaCurcumin) represents a significant innovation. This formulation enhances curcumin's bioavailability by at least 50-fold compared to conventional curcumin, ensuring more effective delivery and therapeutic outcomes. The nanomicellar encapsulation also provides stability and consistent curcuminoid content for up to 24 months, making it a reliable option for clinical use.

Table 5
Mean (95 %CI) of sexual function domain scores at base and post-treatment in dienogest plus curcumin and dienogest.

		Dienogest plus curcumin ($n = 42$) [€]	Dienogest ($n = 43$)				
					95 % CI		*p*
FSFI domain scores		**Mean ± SD**	**Mean ± SD**	Diff [#]	**Lower**	**Upper**	
Desire	Pre	3.23 ± 0.80	3.44 ± 0.62	−0.2	−0.52	0.1	0.184[†]
	Post	4.18 ± 0.58	3.80 ± 0.41	0.4	0.2	0.61	<0.001[§]
	Change	0.92 ± 0.87	0.36 ± 0.62	0.56	0.23	0.89	0.001
Arousal	Pre	3.20 ± 0.83	3.36 ± 0.68	−0.16	−0.48	0.16	0.335[†]
	Post	4.50 ± 0.57	4.22 ± 1.39	0.35	0.01	0.7	0.049[§]
	Change	1.27 ± 0.88	0.85 ± 1.33	0.27	−0.18	0.74	0.231
Lubrication	Pre	3.48 ± 0.79	3.79 ± 0.71	−0.3	−0.63	0.01	0.064[†]
	Post	4.94 ± 0.74	4.48 ± 0.58	0.56	0.31	0.82	<0.001[§]
	Change	1.42 ± 0.73	0.69 ± 0.76	0.73	0.41	1.06	<0.001
Orgasm	Pre	3.68 ± 0.83	3.95 ± 0.75	−0.26	−0.61	0.07	0.121[†]
	Post	5.61 ± 3.28	4.68 ± 0.51	1.06	−0.02	2.16	0.056[§]
	Change	1.90 ± 3.11	0.73 ± 0.75	1.16	0.19	2.14	0.019
Satisfaction	Pre	4.09 ± 1.08	4.29 ± 0.93	−0.2	−0.63	0.22	0.351[†]
	Post	5.68 ± 0.75	5.19 ± 0.67	0.52	0.23	0.81	<0.001[§]
	Change	1.55 ± 1.21	0.89 ± 1.01	0.65	0.17	1.14	0.008
Pain	Pre	3.40 ± 0.84	3.56 ± 0.71	−0.15	−0.49	0.17	0.352[†]
	Post	5.15 ± 0.76	4.41 ± 0.65	0.78	0.51	1.06	<0.001[§]
	Change	1.72 ± 0.94	0.85 ± 0.72	0.86	0.5	1.23	<0.001

[€] The missing value (one women in Dienogest plus curcumin group).
[#] Intervention minus control group.
[†] Based on *t*-test.
[§] Based on Linear Mixed-effects model (the included variables were: basic value of dependent variable, treatment type, BMI, age, analgesic usage and stage of endometriosis).

For instance, Strowitzki et al. (2010) conducted a randomized controlled trial (RCT) showing that dienogest significantly reduced pelvic pain scores in patients with endometriosis compared to placebo (Strowitzki et al., 2010). Similarly, another RCT by Harada et al. (2009) reported that dienogest provided superior symptom relief and improved patient-reported outcomes relative to placebo, further supporting its therapeutic benefits (Harada et al., 2009). In our manuscript, we have integrated these findings to contextualize our results. The discussion highlights how the add-on effect of curcumin to dienogest may offer additional benefits beyond what is observed with dienogest alone. Given that dienogest is already an established treatment with proven efficacy against placebo, our focus was on evaluating whether curcumin enhances its effects rather than reestablishing its superiority over placebo.

There is no study similar to ours, and currently, only one trial conducted by Gudarzi et al. provides relevant insights. In their randomized controlled trial, Gudarzi et al. investigated the effects of curcumin capsules on women with endometriosis. The trial, conducted in 2022 at the Shahid Beheshti Infertility Center in Isfahan, Iran, involved 68 participants allocated into intervention and control groups using the blocked randomization method. The intervention group received curcumin capsules (500 mg) twice daily for 8 weeks, while the control group received a placebo with the same dosage. Data were collected using various questionnaires, including the Endometriosis Health Profile, assessments of painful symptoms, and a visual analogue scale. Their results revealed no statistically significant differences between the intervention and control groups in terms of usual pain, pain at its worst, QOL, and visual pain. These findings suggest that the administration of curcumin did not exert a discernible impact on the painful symptoms or QOL of women with endometriosis (Gudarzi et al., 2024).

In comparing the findings of the two clinical trials, significant disparities emerge regarding the efficacy of curcumin in alleviating symptoms associated with endometriosis. We employed a combination therapy of dienogest and curcumin, demonstrated promising results in improving self-reported pain and enhancing various domains of QOL and sexual function. Notably, significant reductions were observed in dysmenorrhea, dyspareunia, chronic pelvic pain, dyschezia, dysuria, low back pain, and sciatica. These findings suggest a potential synergistic effect between dienogest and curcumin in managing endometriosis-related symptoms. In contrast, the second trial conducted solely with curcumin failed to demonstrate significant improvements in pain levels or QOL among women with endometriosis. Despite administering curcumin capsules for the same duration as the combination therapy trial, the outcomes did not exhibit any statistically significant differences between the intervention and control groups. This stark inconsistency raises questions regarding the isolated efficacy of curcumin in mitigating endometriosis symptoms, as indicated by the lack of discernible impact on pain levels or QOL measures.

The divergent results between the two trials underscore the importance of considering treatment modalities comprehensively in managing endometriosis. While the combination therapy of dienogest and curcumin yielded promising outcomes in ameliorating symptoms and enhancing QOL, the standalone use of curcumin did not confer similar benefits. This disparity suggests that the inclusion of dienogest may potentiate the therapeutic effects of curcumin, highlighting the potential significance of synergistic pharmacological approaches in addressing the multifaceted nature of endometriosis.

One notable difference between the trials lies in the composition and formulation of the curcumin intervention. While Gudarzi et al. administered curcumin capsules at a dosage of 500 mg twice daily for 8 weeks, our trial utilized SinaCurcumin, a formulation containing 80 mg of curcuminoids encapsulated within nanomicelles. This innovative formulation offers several advantages over traditional curcumin capsules, including enhanced bioavailability and stability. The use of nanomicelles allows for improved solubility and absorption of curcuminoids, potentially leading to more effective therapeutic outcomes (Hatamipour et al., 2019; Liu et al., 2020).

Moreover, the consistent curcuminoid content and size distribution of nanomicelles over an extended period, as demonstrated in our trial, ensure the reliability and longevity of the intervention. The stability of Sina Curcumin's formulation for at least 24 months further underscores its suitability for clinical use (Hassaniazad et al., 2021). By leveraging advanced nanotechnology, our trial offers a novel approach to delivering curcumin, potentially optimizing its therapeutic efficacy in managing endometriosis symptoms. Further research into the comparative effectiveness of different curcumin formulations may provide valuable insights into personalized treatment strategies for individuals with endometriosis.

The hepatotoxicity threshold of curcumin has been a subject of

investigation in both preclinical and clinical studies. Available evidence suggests that curcumin is generally well tolerated, even at high doses. Clinical trials have reported no significant hepatotoxicity at doses up to 12 g/day for short durations (Lao et al., 2006). However, some cases of hepatotoxicity have been reported with prolonged intake or in individuals with preexisting liver conditions (Halegoua-DeMarzio et al., 2023). The dosage used in our study was well below the established safety threshold and aligns with previous research demonstrating curcumin's favorable safety profile. Additionally, liver function was monitored throughout the study to ensure participant safety. Therefore, the risk of hepatotoxicity at the administered dose is minimal and does not raise safety concerns in our cohort.

The mechanisms underlying the observed benefits of curcumin supplementation in endometriosis are likely multifactorial. Curcumin is known for its anti-inflammatory and antioxidant properties, which may complement the pharmacological actions of dienogest in reducing inflammation and pain (Peng et al., 2021; Sun et al., 2018). Additionally, curcumin has been shown to modulate various molecular pathways involved in pain perception and inflammation. By targeting multiple pathways simultaneously, the combination therapy may offer a more comprehensive approach to managing endometriosis-related symptoms.

Research suggests that curcumin may exert its beneficial effects through modulation of various signaling pathways involved in the pathogenesis of endometriosis. One such pathway is the nuclear factor-kappa B (NF-κB) pathway, which plays a crucial role in inflammation and immune response. Curcumin has been shown to inhibit NF-κB activation, thereby reducing the production of pro-inflammatory cytokines and suppressing the inflammatory microenvironment associated with endometriosis. By attenuating inflammation, curcumin may alleviate symptoms such as pelvic pain and dyspareunia, which are characteristic of endometriosis (Banerjee et al., 2023; Chowdhury et al., 2019; Liu et al., 2022).

Additionally, curcumin has been implicated in the regulation of the mitogen-activated protein kinase (MAPK) pathway, which modulates cell proliferation, survival, and apoptosis. Dysregulation of the MAPK pathway has been observed in endometriotic lesions, contributing to their aberrant growth and survival. Curcumin exhibits anti-proliferative and pro-apoptotic effects on endometriotic cells through inhibition of MAPK signaling, thereby impeding lesion progression and promoting regression (Hung et al., 2021; Liczbiński et al., 2020). Furthermore, curcumin may interfere with angiogenesis, a process crucial for the establishment and maintenance of endometriotic lesions, by targeting vascular endothelial growth factor (VEGF) signaling pathways. By targeting multiple signaling cascades implicated in endometriosis pathogenesis, curcumin holds promise as a potential therapeutic agent for managing this complex and debilitating condition (Bo and Wang, 2024; Cao et al., 2017). Fig. 2 summarizes the proposed molecular mechanisms underlying the add-on effect of curcumin for the management of endometriosis.

Our study adds to the growing body of evidence supporting the potential therapeutic value of curcumin in endometriosis management. While further research is needed to elucidate the optimal dosing regimen and long-term effects of curcumin supplementation, our findings provide valuable insights into its potential role as an adjunctive therapy. It is important to acknowledge the limitations of our study, including the relatively small sample size and short duration of follow-up. Long-term randomized clinical trials with larger sample size are needed to confirm the sustainability of the observed benefits and evaluate potential adverse effects associated with the combination therapy.

Furthermore, while self-reported measures provide valuable insights into patients' experiences, objective assessments such as imaging studies or biomarker analyses could provide additional validation of the treatment effects. Future studies incorporating both subjective and objective outcome measures are warranted to provide a comprehensive evaluation of the therapeutic efficacy of the combination therapy.

The findings of our study have important clinical implications for the management of endometriosis. Given the multifaceted nature of the condition and the diverse array of symptoms experienced by patients, a personalized and multidisciplinary approach to treatment is essential. The combination of curcumin and dienogest offers a promising option for patients who may not achieve adequate symptom relief with conventional therapies alone. By targeting pain, QOL, and sexual function

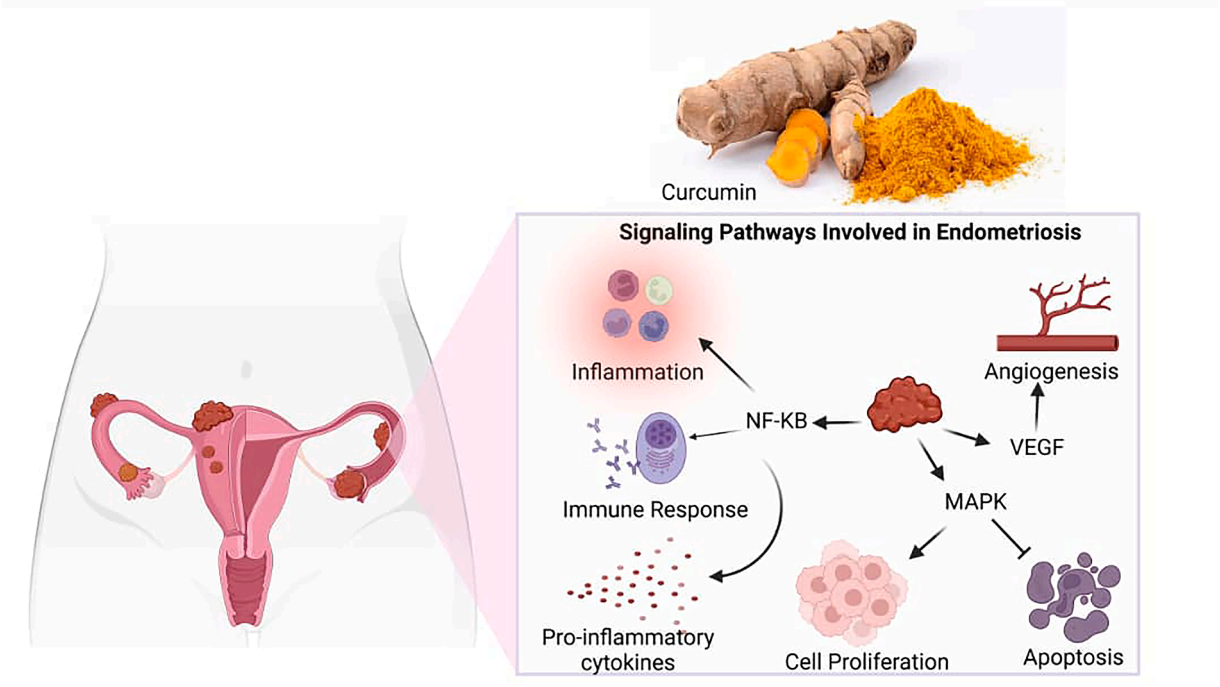

Fig. 2. Proposed molecular mechanisms of curcumin in endometriosis.

simultaneously, the combination therapy addresses the complex and interconnected aspects of endometriosis. Future research should focus on further elucidating the mechanisms of action underlying the observed benefits of curcumin supplementation in endometriosis. This will facilitate the development of more targeted and effective treatment strategies for this challenging condition.

Strengths and limitations

This study possesses several notable strengths. Firstly, it employed a rigorous double-blind, randomized, placebo-controlled design, which is considered the gold standard for clinical trials and minimizes potential biases, thereby enhancing the reliability and validity of the findings. Secondly, the comprehensive assessment of a broad spectrum of outcomes, including pain intensity, QOL, and sexual function, allows for a holistic understanding of the therapeutic effects of the intervention. Thirdly, the utilization of validated measurement tools such as the VAS, WHOQOL-BREF, and the FSFI ensures the accuracy and consistency of the data collected, thereby strengthening the credibility of the results. Additionally, the study leveraged the enhanced bioavailability of nanocurcumin, which is significantly higher compared to conventional curcumin, potentially maximizing the observed therapeutic effects. Finally, the application of robust statistical analysis methods, including multivariable mixed-effects linear regression models and adjustments for key confounders, further bolsters the robustness and validity of the findings.

However, the study also has several limitations that warrant consideration. The relatively short duration of the study, limited to 8 weeks, may not be sufficient to fully capture the long-term effects and safety profile of the combined treatment of dienogest and curcumin. The single-center nature of the trial, conducted at a university hospital, may restrict the generalizability of the findings to broader, more diverse populations. The reliance on self-reported measures for assessing pain and QOL, despite the efforts to mitigate bias through blinding, could introduce potential reporting bias. Lastly, the specific inclusion criteria used may limit the applicability of the results to women with varying stages of endometriosis or different demographic backgrounds, thereby impacting the generalizability of the findings.

Conclusion

In conclusion, our study provides evidence that the addition of curcumin to dienogest is effective in improving pain, QOL, and sexual function in women with endometriosis. These findings have important implications for clinical practice and highlight the potential of combination therapy in optimizing patient outcomes. Moving forward, continued research and clinical trials are needed to validate our findings and explore the broader applicability of curcumin supplementation in the management of endometriosis.

Funding

This work was supported by Zahedan University of Medical Sciences (ZUMS) (grant no. IR.ZAUMS.REC.1401.285).

CRediT authorship contribution statement

Mahjoob Sargazi-taghazi: Writing – review & editing, Writing – original draft, Investigation, Data curation. **Habib Ghaznavi:** Writing – review & editing, Investigation, Data curation. **Roghayeh Sheervalilou:** Writing – review & editing, Investigation, Data curation. **Maryam Razavi:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Mahdi Sepidarkish:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Project administration, Methodology, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

The authors are grateful to all the women who consented to participate.

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