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Original Article

Effect of Curcumin Nanomicelle on the Intensity of Dysmenorrhea in Endometriosis Patients: A Randomized Triple-Blind Placebo-Controlled Trial

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Abstract

Background: Consisting of endometrial tissue outside the uterus, endometriosis is a persistent gynecological illness that causes infertility, pelvic pain, and dysmenorrhea. Curcumin is a bioactive ingredient derived from the spice turmeric and has many pharmacological properties. This study aimed to determine how curcumin affected the severity of dysmenorrhea in patients with endometriosis.

Methods: This research was a triple-blind, randomized-controlled clinical trial conducted on patients referred to the gynecological clinic at the Ghaem and Imam Reza hospitals in Mashhad, Iran. Participants were randomly allocated to the placebo (n=25) and curcumin nanomicelle (n=25) groups. Each patient received two capsules daily (intervention: 40 mg of curcumin nanomicelle; control: placebo) for three months. Before treatment and at the end of the first, second, and third months, the severity of dysmenorrhea, dyspareunia, dyschezia, and chronic pelvic pain was measured using the visual analog scale (VAS). The data were analyzed using SPSS version 26.

Results: The initial and final dysmenorrhea intensity scores differed by 1.66±2.05 and 4.56±1.66 in the placebo and curcumin groups, respectively ($P<0.001$). The placebo and curcumin groups had significantly higher rates of dyspareunia ($P<0.02$), dyschezia ($P<0.02$), and chronic pelvic pain ($P<0.001$).

Conclusion: Although we have limitations, such as the small sample size and restricted generalizability of the results to other populations, our findings demonstrate the possible benefits of curcumin in the improvement of dysmenorrhea, dyspareunia, dyschezia, and chronic pelvic pain in patients with endometriosis.

Keywords: Endometriosis, Dysmenorrhea, Complementary therapy, Herbal medicine, Pelvic pain

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Introduction

Endometrial tissue outside the uterus is a defining feature of endometriosis, a persistent gynecological condition. It is associated with infertility and pelvic discomfort (1). Ectopic endometrial tissue is usually located in the pelvis but can manifest in many other areas of the body. The most common areas of involvement include the ovaries, uterosacral and broad ligaments, fallopian tubes, appendix, and the sigmoid colon (2). Based on epidemiological data, the incidence of endometriosis in a typical population is estimated to be 4-15%, which varies depending on the source of the disease (3). The primary suspicion of its existence is based on clinical symptoms. The symptoms of endometriosis include infertility, dyspareunia, dyschezia, pelvic pain, and dysmenorrhea (4). The gold standard diagnostic method is the observation of endometriotic lesions upon surgery with or without biopsy (5). Endometriosis is the most common cause of secondary

dysmenorrhea (6). Endometriosis' dysmenorrhea usually begins before menstruation and persists during or after this period. This pain is regularly diffused through the pelvis or spread over the back, and may be accompanied by pressure in the rectum, nausea, and transient diarrhea (7). It is hypothesized that the mechanism of dysmenorrhea in endometriosis patients is related to prostaglandins (PGs) because of their higher concentration in the menstrual blood of these patients (8). A study by Bulletti et al revealed that uterine contractions had higher frequency, amplitude, and basal pressure tone in women with endometriosis (9). Hence, severe dysmenorrhea in women with endometriosis may be a consequence of abnormal contractions of the uterus. Although many chemical drugs are used to reduce the intensity of endometriosis' dysmenorrhea, their consumption has been limited due to a wide range of adverse effects (10). Hormonal therapy, including combined estrogen-progestin contraceptives, progestogens, and gonadotropin-releasing hormone (GnRH) analogues, seeks to restrict ovarian hormone production to minimize endometriotic lesion activity. However, these treatments typically provide temporary relief, with symptoms recurring after therapy is ceased. Furthermore, not all patients have adequate pain relief throughout treatment (11). Long-term use of hormonal treatments can lead to side effects such as bone density loss, mood changes, weight gain, and vasomotor symptoms. For instance, GnRH analogs induce a hypoestrogenic state, potentially causing menopausal-like symptoms and decreasing bone mineral density (12). Given these limitations, there is a compelling need to explore alternative treatments that offer effective symptom relief with fewer side effects. Alternatively, herbal medicine and complementary products such as ginkgo, magnesium pyrrolidone, saffron, St. John's Wort, soy, and vitamin E are being administered extensively in many inflammatory conditions, such as premenstrual syndrome (PMS) and dysmenorrhea (13). Turmeric is the source of curcumin, a bioactive substance that belongs to the Zingiberaceae family. Curcumin has many pharmacological properties, including anti-inflammatory, antineoplastic, antioxidant, cardioprotective, immunomodulatory, lipid-lowering, antidepressant, and analgesic (14-16). Curcumin's therapeutic use has been affected by its low bioavailability due to low solubility and rapid metabolism. Curcumin's bioavailability and therapeutic efficacy have been improved using nanotechnology-based delivery technologies, such as nanomicelle. Nano-micelles can enhance curcumin's solubility, stability, and absorption, potentially improving its therapeutic efficacy in endometriosis patients (17). It is interesting to note that curcumin has been demonstrated to suppress PG formation by inhibiting the cyclooxygenase-2 (COX-2) enzyme (18). Additionally, the clinical effects of curcumin on endometriosis have not been previously investigated. This study was thus carried out to examine the impact of curcumin nanomicelle on the severity of dysmenorrhea and other symptoms, including dyspareunia, dyschezia, and chronic pelvic pain in patients with endometriosis, based on the role of PGs in endometriosis' dysmenorrhea.

Methods

Study Design

This study was a triple-blind, randomized clinical trial with control and intervention groups, performed from December 2020 to November 2021, at the gynecology clinic of Ghaem and Imam Reza hospitals affiliated with the Mashhad University of Medical Sciences, Mashhad, Iran. To report this clinical research, we followed the CONSORT reporting criteria (19).

Study Population

Sixty patients with endometriosis were assessed, and 50 patients were included in the study based on inclusion and exclusion criteria.

The following were the requirements for inclusion: diagnosis of endometriosis based on ultrasound, magnetic resonance imaging (MRI), or surgery (based on persistent cyst or typical endometriosis profile); complaints of dysmenorrhea; and age of 15-45 years. The exclusion criteria were treatment with GnRH agonist or antagonist drugs, other medical treatments such as dinogest and contraceptives, the intention to become pregnant, and any major allergic reaction related to curcumin.

Study Protocol

Patients who qualified were divided into two groups randomly: the curcumin nanomicelle group and the placebo group. The intervention group received two oral capsules (red oval soft gel capsules) of curcumin nanomicelle (40 mg) (Cinacurcumin, Minoo Pharmaceutical Company, Tehran, Iran) daily for three months. The encapsulation percentage of curcumin in the formulation was approximately 100%. In addition, it has been demonstrated that the bioavailability of curcumin nanomicelle is significantly higher than that of other formulations (20). The control group was concurrently treated with two placebo capsules (red oval soft gel capsules) per day. Patients in both groups only received non-steroidal anti-inflammatory drugs (NSAIDs) as a standard treatment in cases of extreme pain because they had low stages of endometriosis. We measured characteristics such as age (year), BMI, marital status, parity status, dysmenorrhea, dyspareunia, dyschezia, and pain severity between periods at baseline. The severity of dysmenorrhea, dyspareunia, dyschezia, and pain severity between periods was measured by the visual analog scale (VAS) score. A gynecologist used the VAS score to assess the severity of dysmenorrhea, dyspareunia, dyschezia, and pain severity between periods on the first day of

menstruation before beginning treatment. The VAS uses a 10-cm horizontal line with a score range of 0–10. Zero traditionally denotes "no pain at all," while 10 implies the "worst pain" that is physically possible. The treatment began on that day (the first day of menstruation). The gynecologist was trained to use the VAS scale consistently by participating in educational workshops and simulation-based trainings. We conducted workshops that provided comprehensive education on the VAS, including its purpose, application, and interpretation. Furthermore, simulation-based training provided an excellent opportunity for the gynecologist to improve her skills in administering the VAS. By participating in realistic scenarios with standardized patients, the practitioner developed her communication skills, gained confidence, and ensured adherence to standardized procedures, resulting in better patient outcomes.

During the three months of treatment, patients were evaluated according to the intensity of dysmenorrhea, dyspareunia, dyschezia, and pain severity between periods at 4-time points, before the treatment, at the end of the first month, at the end of the second month, and finally, at the end of the third month (the last appointment and the end of the treatment). However, detecting the differences within each study group over time was also important and was assessed. To detect any overall differences within each group, we calculated the difference between initial and final measurements.

Outcome

The severity of dysmenorrhea was assessed and compared with the placebo group as a primary endpoint, and the severity of dyspareunia, dyschezia, and chronic pelvic pain was measured and compared with the placebo group as our secondary endpoints. Additionally, medication adherence was assessed at each visit.

Randomization and Blinding

The random allocation sequence was created using a computer-generated randomized list that was obtained from the randomization.com website. The Minoo Company packed bottles with a placebo and nanocurcumin, then numbered them (a number between 1 and 50) according to the allocation order. The clinical pharmacist or physician, depending on which patient met the inclusion criteria, gave the boxes to them. The physician assessed the patients while they were receiving treatment. The clinical pharmacist handled the data entry and gathering into the SPSS program. The patients' group assignment was undisclosed to the clinicians. Before the clinical pharmacist analysis of the data, grouping data were added to the SPSS file according to the allocation sequence, but only as group 1 or 2, by a third party who was not involved in the investigation. As a result, the clinical pharmacist was unaware of the patient's allocation to treatments or placebos. Following the analysis, the third party defined codes 1 and 2. Thus, the patient's group assignment was unknown to the physician, the clinical pharmacist, or the surgery specialist.

Sample Size Calculation and Statistical Analysis

Since this study was intended to be a pilot study, the sample size was determined using the formula below. Based on the findings of the Warzecha et al study (5), the sample size was determined to be 22 by assuming equal variances and taking into account a two-level reduction in dysmenorrhea pain that was substantial in the view of our experts. Statistical analysis was performed using SPSS version 26. Descriptive statistics (mean and standard deviation) were calculated for age, body mass index (BMI), marital status, and parity. Categorical variables were compared with the chi-square test. The Kolmogorov-Smirnov test was used to assess the normality of the data. To compare the mean or median between two independent groups, the independent t-test and the Mann-Whitney U-test were utilized, respectively. Any discrepancies between related means or medians were found using the Friedman test or repeated measures ANOVA. Statistical significance was set at $P \leq 0.05$, which was considered statistically significant.

$$n_1 = n_2 = \frac{\left(S_1^2 + S_2^2\right)\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)^2}{\left(\bar{X}_1 - \bar{X}_2\right)^2}$$

Results

Population Study

The present study was conducted on 50 patients; 25 were treated with curcumin in the intervention group, and 25 were treated with a placebo. All of these patients fulfilled the trial criteria, were enrolled in the study by protocol, and completed the whole three months of trial duration (Figure 1). We measured characteristics such as age, BMI, marital status, parity status, dysmenorrhea, dyspareunia, dyschezia, and pain severity between periods at baseline (Table 1). At baseline, there were no notable variations among the patients.

Comparison of Dysmenorrhea Severity Between Placebo and Curcumin Nanomicelle

Before intervention, we found no discernible difference in the severity of dysmenorrhea between the groups receiving curcumin nanomicelle and a placebo. However, pain levels in the intervention group, as mentioned in Table 2, decreased over time. In the placebo group, the pain severity decreased during the study, but not as much as in the patients treated with curcumin nanomicelle. Nevertheless, the reduction was statistically significant in the placebo group too. In addition, differences between

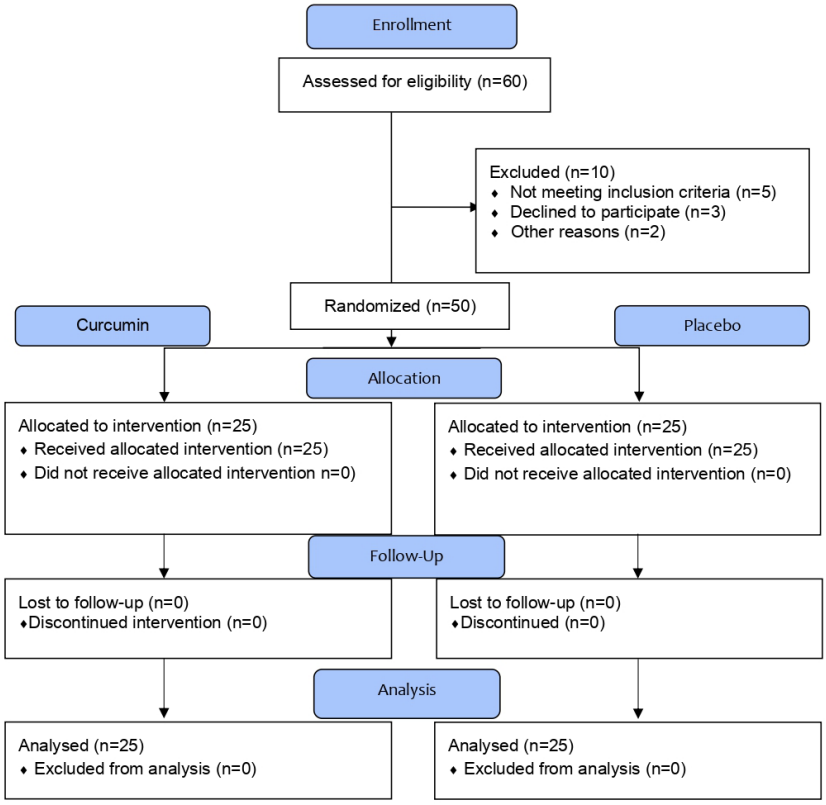

Figure 1. Flow diagram of the trial

Table 1. The Baseline characteristics of the participants

Characteristics	Group		*P* value[a]
	Placebo (n=25) Mean±SD	Curcumin (n=25) Mean±SD	
Age (year)	31.88±6.13	32.36±6.21	1
BMI (kg/m²)	25.36±3.23	24.76±3.58	0.57
Marital status			
Married	18 (72%)	19 (76%)	0.74
Single	7 (28%)	6 (24%)	
Parity status			
No child	15 (60%)	13 (52%)	0.56
With children (1-4)	10 (40%)	12 (48%)	
Dysmenorrhea score	7±1.44	6.88±1.48	0.81
Dyspareunia score	5.9±2.62	6.08±1.84	0.36
Dyschezia score	5±3.16	6.08±1.65	0.41
Chronic pelvic pain score	5.11±144	5.38±1.62	0.70

[a] Calculated by the Mann-Whitney U test; * Significant differences vs. placebo group (*$P<0.05$).

the initial and final scores were measured. Interestingly, we found that curcumin nanomicelle had a significantly greater effect on reducing the severity of dysmenorrhea than the placebo group ($P<0.001$) (Table 3, Figure 2).

Comparison of Dyspareunia Severity Between Placebo and Curcumin Nanomicelle

In examining patients at baseline regarding pain during intercourse or dyspareunia, we found no substantial difference between patients in the intervention and placebo groups. After the administration of curcumin, the patient's pain level in the intervention group decreased gradually. Curcumin significantly decreased dyspareunia at the end of the study compared to the initial examination. Also, in the placebo group, we observed a reduction in pain levels during the study (Table 2). Ultimately, we demonstrated that dyspareunia reduction was substantially superior in the curcumin group than in the placebo group ($P<0.02$) (Table 3 Figure 3).

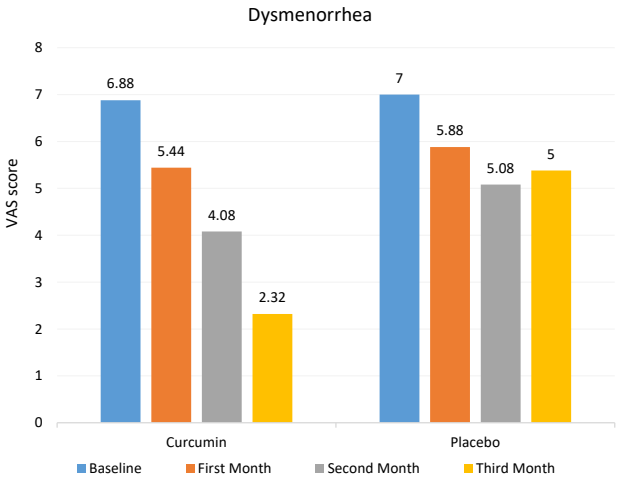

Figure 2. Dysmenorrhea severity in placebo and curcumin nanomicelle groups

Table 2. Dysmenorrhea, dyspareunia, dyschezia, and chronic pelvic pain severity in placebo and curcumin nanomicelle groups

	Dysmenorrhea		Dyspareunia		Dyschezia		Chronic pelvic pain	
	Placebo (n = 25) (Median ± IQR)	Curcumin (n = 25) (Median ± IQR)	Placebo (n = 18) (Median ± IQR)	Curcumin (n = 19) (Median ± IQR)	Placebo (n = 25) (Median ± IQR)	Curcumin (n = 25) (Median ± IQR)	Placebo (n = 25) (Median ± IQR)	Curcumin (n = 25) (Median ± IQR)
First month	5.88 ± 1.71	5.44 ± 1.47	4.36 ± 2.20	4.31 ± 1.79	4.38 ± 3.62	4.15 ± 1.86	3.89 ± 1.62	3.67 ± 1.88
Second month	5.08 ± 1.86	4.08 ± 1.60	3.18 ± 1.25	2.62 ± 2.10	3.88 ± 1.80	1.92 ± 1.93	4 ± 1.76	1.57 ± 1.53
Third month	5.38 ± 1.86	2.32 ± 1.40	2.73 ± 1.42	1.38 ± 1.80	3.25 ± 1.48	1.31 ± 1.70	4.11 ± 2.49	1.10 ± 1.44
P value[a]	< 0.001*	< 0.001*	< 0.01*	< 0.001*	< 0.43	< 0.001*	< 0.01*	< 0.001*

[a] Calculated by the Friedman test; * Significant differences vs. placebo group (*$P < 0.05$).

Table 3. Comparison of initial and final difference scores between the placebo and curcumin groups

Initial and final difference score	Placebo (Median ± IQR)	Curcumin (Median ± IQR)	*P* value[a]
Dysmenorrhea	1.66 ± 2.05	4.56 ± 1.66	< 0.001*
Dyspareunia	2.36 ± 2.78	4.69 ± 1.54	< 0.02*
Dyschezia	1.75 ± 2.43	4.76 ± 2.31	< 0.02*
Chronic pelvic pain	1 ± 1.88	4.28 ± 1.79	< 0.001*

[a] Calculated by the Mann-Whitney U test; * Significant differences vs. placebo group ($P < 0.05$).

Comparison of Dyschezia Severity Between Placebo and Curcumin Nanomicelle

Dyschezia or *pain and difficulty during defecation severity were not statistically different at baseline between the intervention and control groups*. Interestingly, pain reduction during the study period was statistically significant in the curcumin group ($P < 0.001$). However, patients in the placebo group experienced less and non-significant pain reduction during the study period ($P < 0.43$) (Table 2). Furthermore, we compared the amount of pain reduction between the placebo and the intervention groups. Finally, it was demonstrated that curcumin significantly decreased dyschezia compared to the placebo group ($P < 0.02$) (Table 3, Figure 4).

Comparison of Chronic Pelvic Pain Between Placebo and Curcumin Nanomicelle

The chronic pelvic pain in the curcumin group and the placebo group at baseline was not considerably different. Nevertheless, after curcumin treatment, the pain was reduced in the intervention group and significantly improved compared to the initial measurements. Conversely, in the placebo group, we observed a non-significant increase in pain levels during the study (Table 2). In addition, the difference in initial and final scores was measured, and the intervention group showed a significantly greater reduction in chronic pelvic pain than the placebo group ($P < 0.001$) (Table 3, Figure 5).

Discussion

This study presents valuable results regarding the effects of curcumin nanomicelle on the intensity of dysmenorrhea pain in patients with endometriosis. Based on our findings,

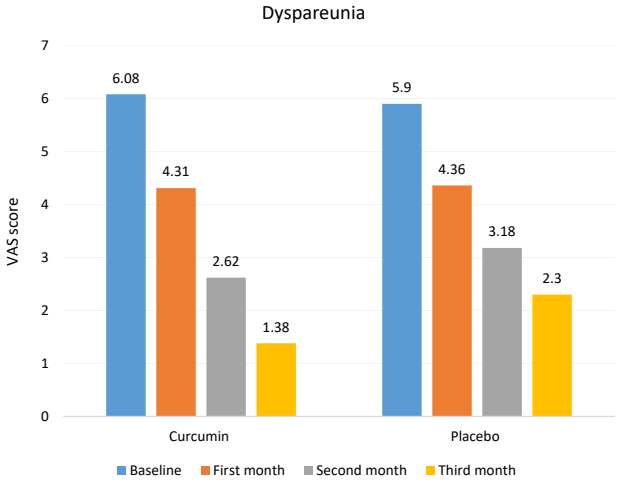

Figure 3. Dysmenorrhea severity in placebo and curcumin nanomicelle groups

patients with endometriosis and dysmenorrhea after three months of treatment with curcumin nanomicelle showed significant reductions in the mean scores of dysmenorrhea, dyspareunia, dyschezia, and chronic pelvic pain in comparison with the control group. To the best of our knowledge, this is the first study to investigate the effect of curcumin on dysmenorrhea intensity in patients with endometriosis.

Regarding the pathophysiology of endometriosis, some ideas have been put out; the most commonly recognized of them is Sampson's implantation theory. According to this opinion, retrograde menstruation is the mechanism by which some endometrial cells enter the peritoneal cavity (21). Therefore, the adhesion and multiplication of endometrial cells, cellular invasion, and angiogenesis are crucial in the development of endometriosis (22). The pathophysiology of endometriosis involves several inflammatory and growth factors, angiogenic stimulants, and adhesion molecules, including vascular endothelial growth factor (VEGF), transforming growth factor-β (TGF-β), interleukin-6 (IL-6), IL-8, and tumor necrosis factor-α (TNF-α) (21). Curcumin is an anti-inflammatory agent that has recently demonstrated additional properties such as anti-angiogenic, anti-metastatic, anti-mutagenic, and hormonal regulatory (23,24). A study performed by Zhang et al analyzed the impact of curcumin on endometrial cells in patients with endometriosis. In this

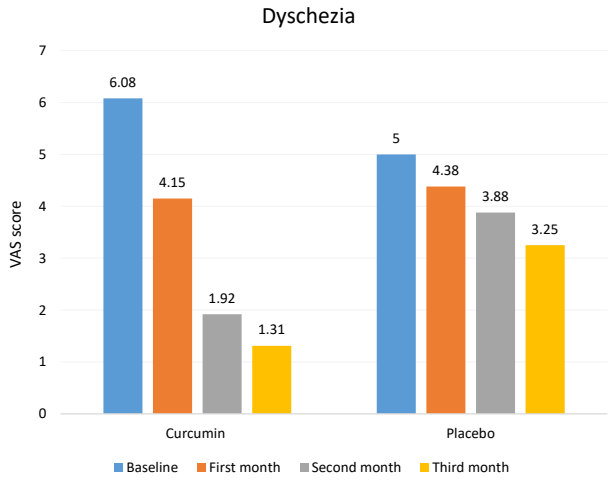

Figure 4. Dyschezia severity in placebo and curcumin nanomicelle groups

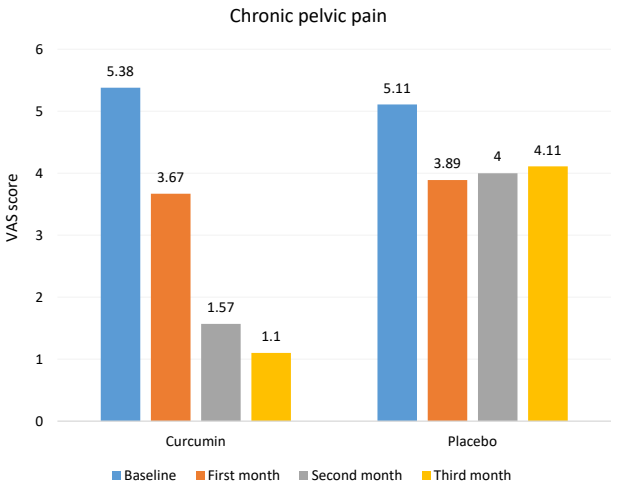

Figure 5. Chronic pelvic pain severity in placebo and curcumin nanomicelle groups

study, endometriotic epithelial cells, normal endometrial stromal cells, normal epithelial cells, and endometriotic stromal cells were isolated from premenopausal women who had undergone hysterectomy and were fixed in 10% formalin. Then, the cells were examined for pathology and were excluded from the study in case of malignancy. Cells estradiol value and the effect of curcumin on cell proliferation were assessed. Finally, they found that curcumin inhibited cell proliferation by reducing the amount of estradiol in endometrial cells (25). Another study investigated the effect of curcumin on apoptosis and the progression of endometriosis in BALB/c mice. They carried out a three-day pretreatment of curcumin before the induction of peritoneal endometriosis, and then, a five-day treatment with curcumin or celecoxib. They reported that the development of peritoneal endometrial glands significantly decreased in the curcumin group. They also reported an increase in the ratio of B-cell lymphoma protein 2 (Bcl-2)-associated X (Bax), elevation of mitochondrial apoptotic factors such as caspase-9 and cytochrome-c, and upregulation of anti-tumor factors like P53 in the curcumin group compared with controls (26). Furthermore, many other studies have reported similar results in terms of the effects of curcumin on the proliferation and apoptosis of endometrial cells (27-29). Angiogenesis and a new blood supply are important factors in the development of endometriosis. Interestingly, it has been reported that the angiogenic activity and concentration of angiogenic factors such as VEGF are substantially higher in women with endometriosis (30,31). Some studies have explored the antiangiogenic effects of curcumin in rodent models of endometriosis. It has been stated that curcumin can repress the micro-vessel density (MVD) in the ectopic endometrium and reduce VEGF in the serum and ectopic endometrium, while it had no substantial impact on MVD in the utopic endometrium in another investigation (32-34). Inflammatory agents, such as TNF-α, IL-1, IL-6, IL-8, and TGF-β, play a crucial role in the pathogenesis and progression of endometriosis (35). Curcumin has been identified as a novel anti-inflammatory agent, and its effects have been proven in many studies (36,37). In a previous study, curcumin significantly decreased the secretion of IL-6, IL-8, *Monocyte chemoattractant protein-1* (MCP-1), and nuclear factor kappa-light-chain-enhancer of activated B cells (*NF-κB*) in human ectopic endometriotic stromal cells (38). Curcumin mainly reduces inflammation by blocking the NF-κB signaling pathway, which is a major inflammatory regulator. TNF-α and IL-6 are two pro-inflammatory cytokines that are transcriptionally triggered by NF-κB activation. By blocking the phosphorylation and degradation of IκBα, curcumin inhibits NF-κB activation and prevents NF-κB from translocating to the nucleus. This results in reduced expression of TNF-α, IL-6, and other inflammatory mediators (38- 40). In another study conducted by Soetikno et al in rats, curcumin treatment significantly reduced the abundance of COX-2, NF-κB, TNF-α, and *malondialdehyde* (MDA) levels (41). A randomized, double-blinded clinical trial consisting of 70 patients demonstrated that curcumin has a substantial effect on PMS symptoms, probably due to its anti-inflammatory effects (42). In another randomized controlled study of 76 female patients treated with curcumin for three months, curcumin had a brilliant effect on PMS symptoms and dysmenorrhea in comparison with the control group (43). In addition, a triple-blind, placebo-controlled clinical trial investigated the effects of curcumin on menstrual patterns, PMS, and dysmenorrhea. They enrolled 124 patients and divided them into two groups. They treated patients in the intervention group with curcumin for three months. Eventually, they reported a significant improvement resulting from curcumin in PMS symptoms and dysmenorrhea (44). Furthermore, another clinical trial reported that the co-administration of curcumin and mefenamic acid could have a significant effect on primary dysmenorrhea (45). Specifically, many studies

have reported that curcumin represses the synthesis of PGs through inhibition of the COX-2 enzyme (18). Furthermore, it has been mentioned that the main mechanism of dysmenorrhea in endometriosis patients is related to PGs because of their higher concentration in the menstrual blood of these patients (46). In this study, we investigated the effect of curcumin on the intensity of dysmenorrhea in endometriosis patients, which showed significant reductions in the mean scores of dysmenorrhea, dyspareunia, dyschezia, and chronic pelvic pain compared to those in the control group.

Nonetheless, we had some limitations, such as a small sample size due to the limited number of patients who fulfilled the inclusion criteria and the shortness of the follow-up period. A longer follow-up period and combining curcumin with other treatments would reveal more accurate results about the efficacy and adverse effects of curcumin nanomicelle on patients. Apart from that, demographic factors such as age, marital status, parity, and education level can significantly impact the prevalence and severity of dysmenorrhea and other endometriosis-related symptoms. These demographic variables can influence both the perception and reporting of symptoms, potentially affecting the outcomes of interventions like curcumin nanomicelle (47). Although there were no significant differences between the placebo and intervention groups in terms of age, marital status, parity, and BMI at baseline, we did not record education level. Future research should include education level as a compounding component. Finally, our study's limitations include the limited generalizability of our findings to other populations due to the small sample size and rigid inclusion criteria. Our study had several strengths, including a randomized, triple-blind, and placebo-controlled design and three months of treatment with curcumin nanomicelle as an identified and standard active turmeric plant constituent.

Conclusion

The results of this randomized, triple-blind, placebo-controlled clinical trial indicated that patients with endometriosis who used two oral capsules (40 mg) of curcumin nanomicelle daily for three months reported a significant reduction in the severity of dysmenorrhea, dyspareunia, dyschezia, and chronic pelvic pain based on the VAS score. Although the severity reduction was significant in the placebo groups, the reduction was significantly greater in the curcumin groups than in the placebo groups. To assess the impact of curcumin on patients with endometriosis more accurately, more clinical trials with larger sample sizes and longer follow-ups are necessary.

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Authors' Contribution

Conceptualization: Shima Hatami, Malihe Amirian.
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Funding acquisition: Malihe Amirian.
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Methodology: Leli Hafizi.
Project administration: Shima Hatami, Navid Omidkhoda.
Resources: Malihe Amirian.
Software: Shabnam Niroumand.
Supervision: Malihe Mahmoudinia, Amir Hooshang Mohammadpour.
Validation: Malihe Mahmoudinia, Amir Hooshang Mohammadpour, Maliheh Amirian.
Visualization: Navid Omidkhoda, Amir Hooshang Mohammadpour.
Writing–original draft: Navid Omidkhoda.

Competing Interests

The authors declare that they have no conflict of interest.

Ethical Approval

The Ethics Committee of Mashhad University of Medical Sciences approved the study (IR.MUMS.MEDICAL.REC.1400.282) and was registered in the Iranian Registry of Clinical Trials (IRCT20201121049457N1).

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