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Research Article

Effect of Nanocurcumin on Ferritin Expression in Ovarian Granulosa Cells in an Experimental Murine Model of Endometriosis

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Abstract | Endometriosis is associated with iron accumulation and oxidative stress in the ovarian microenvironment, which may alter ferritin expression in granulosa cells and impair follicular function. Because ferritin is an adaptive iron-sequestration protein, changes in its expression may reflect altered cellular responses to iron-related stress rather than direct changes in iron burden. This study evaluated the effect of nanocurcumin on ferritin expression in ovarian granulosa cells in a murine model of endometriosis. Twenty-eight female mice were randomly assigned into four groups (n = 7/group): an untreated endometriosis control group (C+) and three treatment groups receiving nanocurcumin at doses of 2.5, 5, or 10 mg/kg body weight for 14 days. Following nanocurcumin treatment, superovulation was induced, and ovarian tissues were subsequently collected for immunohistochemical evaluation of ferritin expression in granulosa cells using a semi-quantitative immunoreactive score (IRS). Data were analyzed using the Kruskal-Wallis test followed by Dunn's post hoc test with Bonferroni correction. Ferritin expression differed significantly among groups (p = 0.001). The 10 mg/kg body weight group showed significantly lower ferritin expression than the untreated control group, whereas the lower-dose groups showed lower scores without statistically significant pairwise differences after correction. In conclusion, nanocurcumin was associated with reduced ferritin expression in ovarian granulosa cells, with the clearest effect observed at the highest dose. As ferritin reflects an indirect cellular response to iron-related stress, future investigations should incorporate direct assessments of iron metabolism, oxidative injury, and ferroptosis-associated markers to better define the mechanism underlying this observation. These findings may support future research relevant to SDG 3: Good Health and Well-being, particularly in the development of non-hormonal approaches to improve reproductive health in endometriosis.

Keywords | Endometriosis, Nanocurcumin, Ferritin, Granulosa cells, Ovary, Good health and well-being

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INTRODUCTION

Endometriosis is a chronic inflammatory disorder characterized by the presence of endometrial-like tissue outside the uterine cavity, most commonly on pelvic organs, and is frequently associated with pelvic pain and infertility (Giudice and Kao, 2004). The condition affects approximately 10% of women of reproductive age and remains a major challenge in reproductive medicine because of its multifactorial pathogenesis and variable clinical presentation. Although the exact mechanisms underlying endometriosis are not yet fully understood,

increasing evidence indicates that the disease is sustained by a complex interaction among hormonal imbalance, chronic inflammation, oxidative stress, and altered immune responses (Kobayashi *et al*., 2009; Wyatt *et al*., 2023).

One of the important pathogenic features of endometriosis is repeated cyclic bleeding from ectopic endometrial lesions, which results in the accumulation of hemoglobin degradation products and free iron in the peritoneal cavity and surrounding tissues (Defrère *et al*., 2008; Kobayashi *et al*., 2009). Excess iron promotes reactive oxygen species generation through redox cycling and thereby amplifies oxidative stress, inflammatory signaling, and cellular injury (Kobayashi *et al*., 2009; Wyatt *et al*., 2023). This iron-rich microenvironment has been implicated not only in the persistence of endometriotic lesions but also in the impairment of ovarian function (Patel *et al*., 2025; Sanchez *et al*., 2014).

Granulosa cells are essential components of the ovarian follicle and play central roles in follicular growth, steroidogenesis, oocyte maturation, and maintenance of female fertility. Because of their high metabolic activity, granulosa cells are particularly vulnerable to oxidative and iron-related stress. Disruption of granulosa cell homeostasis may adversely affect the follicular microenvironment and compromise oocyte competence. In endometriosis, increased iron deposition and oxidative stress within ovarian tissue have been associated with granulosa cell dysfunction, mitochondrial damage, ferroptosis, and reduced reproductive potential (Woo *et al*., 2020; Lin *et al*., 2020; Ni *et al*., 2022).

Ferritin is the major intracellular iron-storage protein and serves as an important regulator of iron homeostasis by sequestering excess iron in a non-toxic form. Increased ferritin expression is generally regarded as a protective cellular response to iron overload and oxidative stress (Wyatt *et al*., 2023). Therefore, ferritin expression in ovarian granulosa cells may provide useful information regarding the degree of iron-related cellular stress in the ovarian microenvironment under endometriosis conditions (Patel *et al*., 2025; Woo *et al*., 2020).

Curcumin, a natural polyphenolic compound derived from *Curcuma longa*, has been widely recognized for its antioxidant, anti-inflammatory, and metal-chelating properties (Aggarwal and Harikumar, 2009; Hewlings and Kalman, 2017). Its iron-modulating activity is partly related to its ability to interact with metal ions, including ferric iron (Borsari *et al*., 2002; Jiao *et al*., 2006). However, the therapeutic application of conventional curcumin is limited by poor aqueous solubility and low bioavailability (Hewlings and Kalman, 2017). Nanocurcumin, a nanoparticle formulation of curcumin, has been developed to improve its stability, absorption, and tissue distribution. Previous studies have suggested that nanocurcumin may exert beneficial effects in inflammatory and oxidative stress-related disorders, but its role in modulating ferritin expression in ovarian granulosa cells during endometriosis remains insufficiently investigated (Hewlings and Kalman, 2017; Jiao *et al*., 2006).

Despite growing evidence that iron overload contributes to granulosa cell dysfunction in endometriosis, it remains unclear whether nanocurcumin can modulate ferritin immunoreactivity in ovarian granulosa cells under these conditions. Most previous studies have focused on the general antioxidant and anti-inflammatory effects of curcumin, whereas its association with ferritin expression in ovarian granulosa cells in endometriosis has not been clearly examined. Therefore, this study aimed to evaluate whether nanocurcumin administration is associated with altered ferritin expression in ovarian granulosa cells in a murine model of endometriosis. We hypothesized that nanocurcumin treatment would be associated with lower ferritin immunoreactivity compared with the untreated endometriosis group.

MATERIALS AND METHODS

Study design and experimental animals

This study employed an experimental laboratory design with a completely randomized arrangement. Twenty-eight healthy female Mus musculus, aged 8–10 weeks and weighing 20–25 g, were obtained from the Laboratory Animal Facility, Faculty of Veterinary Medicine, Universitas Airlangga, Surabaya, Indonesia. Before experimentation, all animals were acclimatized for 7 days under standard laboratory conditions (22±2 °C; 12 h light/12 h dark cycle) with ad libitum access to a commercial pellet diet and water. Health status was evaluated before inclusion on the basis of general activity, body condition, coat appearance, feed and water intake, and the absence of visible external abnormalities or signs of illness. Estrous cycle synchronization was not performed before randomization because this study was designed to evaluate the overall effect of nanocurcumin on ferritin expression in ovarian granulosa cells under endometriosis-like conditions, rather than to assess estrous-stage-specific hormonal changes. Avoiding synchronization also minimized additional hormonal manipulation that could potentially influence ovarian inflammatory responses, iron-related stress, and ferritin regulation. To reduce potential bias, animals were randomly assigned to each experimental group under identical housing, feeding, and handling conditions.

Animals were randomly allocated by simple randomization into four groups (n= 7 per group): an untreated endometriosis control group (C+) and three treatment groups receiving

nanocurcumin at doses of 2.5 mg/kg body weight (T1), 5 mg/kg body weight (T2), and 10 mg/kg body weight (T3). No a priori power analysis was performed; therefore, the study should be interpreted as an exploratory preclinical study.

Materials and nanocurcumin preparation

Reagents used in this study included curcumin (Sigma-Aldrich, product no. 8.20354), 0.9% NaCl, povidone-iodine, ketamine hydrochloride (Ketamil®), xylazine hydrochloride (Rompun®), 10% neutral buffered formalin, pregnant mare serum gonadotropin (PMSG; Folligon®, Intervet, Boxmeer, The Netherlands), and human chorionic gonadotropin (hCG; Chorulon®, Intervet, Boxmeer, The Netherlands). Nanocurcumin was administered orally by gastric gavage once daily for 14 consecutive days according to the assigned dose in each treatment group.

Nanocurcumin characterization

The nanocurcumin formulation was characterized before use by dynamic light scattering (DLS) and scanning electron microscopy (SEM). The mean particle size was 34.2 nm, with a polydispersity index (PDI) of 0.28 and a zeta potential of –22.5 mV, indicating a relatively stable and monodisperse nanosuspension. Surface morphology was evaluated by SEM to verify the nanoscale characteristics of the formulation before administration.

Induction of experimental endometriosis

Experimental endometriosis was induced according to the previously described protocol of Hendarto *et al.* (2014), with minor modifications. Briefly, all animals underwent surgical induction of endometriosis under general anesthesia using ketamine hydrochloride (100 mg/kg body weight, intraperitoneally) combined with xylazine hydrochloride (10 mg/kg body weight, intraperitoneally). After a midline abdominal incision, uterine tissue fragments were surgically implanted onto the peritoneal wall to establish ectopic endometrial lesions in the peritoneal cavity. The abdominal incision was closed using 3-0 silk and chromic catgut sutures. Because this study was designed to compare treated and untreated endometriosis animals, no negative sham-operated group was included. A schematic overview of the experimental design is presented in Figure 1.

Superovulation and ovarian tissue collection

At the end of the 14-day treatment period, superovulation was induced by intraperitoneal administration of 5 IU PMSG, followed 48 h later by 5 IU hCG. Female mice with confirmed vaginal plugs were euthanized 17 h after hCG injection. This time point was selected to obtain periovulatory ovarian tissue for ferritin immunohistochemical evaluation before more advanced post-ovulatory tissue remodeling occurred. Both ovaries were collected immediately and fixed in 10% neutral buffered formalin for histological and immunohistochemical examination.

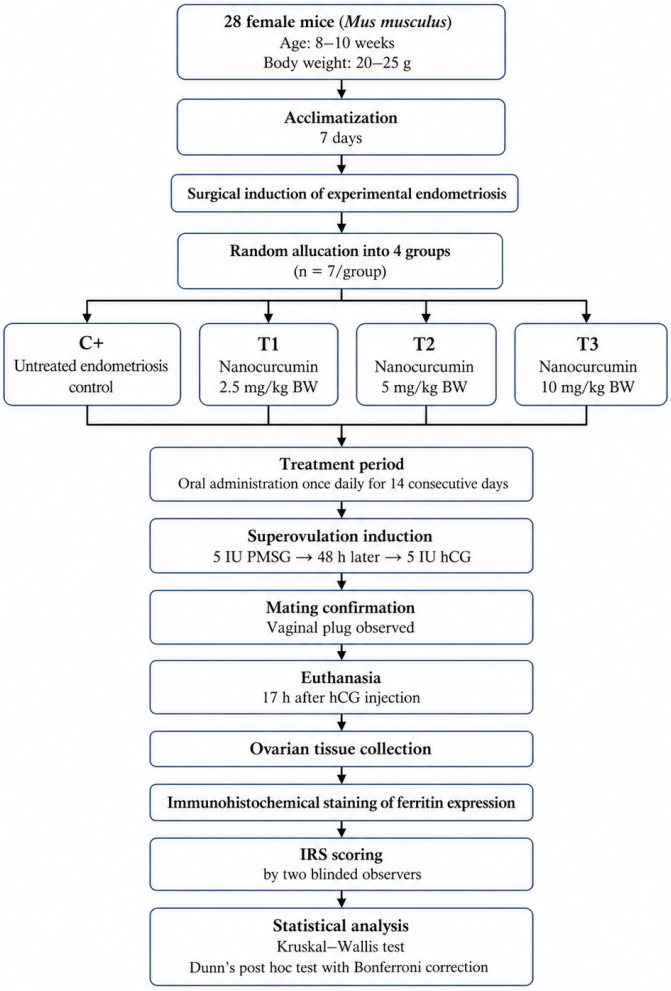

Figure 1: Experimental design of the study. Female mice were acclimatized for 7 days, subjected to surgical induction of experimental endometriosis, and randomly allocated into four groups (n = 7/group): C+ untreated control, T1 nanocurcumin 2.5 mg/kg BW, T2 nanocurcumin 5 mg/kg BW, and T3 nanocurcumin 10 mg/kg BW. Nanocurcumin was administered orally for 14 days, followed by superovulation, ovarian tissue collection, ferritin immunohistochemistry, IRS scoring, and statistical analysis.

Immunohistochemical examination of ferritin expression

Fixed ovarian tissues were processed routinely, embedded in paraffin, and sectioned at 4–5 µm. The sections were deparaffinized in xylene and rehydrated through graded ethanol. Endogenous peroxidase activity was blocked using hydrogen peroxide solution, followed by antigen retrieval according to the manufacturer's instructions. Sections were then incubated with a commercially available monoclonal anti-ferritin primary antibody according to the manufacturer's protocol, followed by incubation with

an appropriate horseradish peroxidase (HRP)-conjugated secondary antibody. Immunoreactivity was visualized using diaminobenzidine (DAB) chromogen, and the sections were counterstained with hematoxylin. Ferritin-positive granulosa cells were identified by brown cytoplasmic staining under light microscopy.

Evaluation of immunoreactivity

Ferritin expression in ovarian granulosa cells was evaluated semi-quantitatively using the Immunoreactive Score (IRS), adapted from Nowak *et al.* (2007). The final IRS was calculated by multiplying the score for the percentage of positive cells (A) by the score for staining intensity (B): IRS = A × B. Score A was defined as follows: 0 = no positive cells; 1 = <10% positive cells; 2 = 11–50% positive cells; 3 = 51–80% positive cells; and 4 = >80% positive cells. Score B was defined as follows: 0 = no color reaction; 1 = low intensity; 2 = moderate intensity; and 3 = high intensity.

At least five non-overlapping microscopic fields were evaluated per ovary at 400× magnification. Scoring was performed independently by two observers who were blinded to group allocation. Any discrepancy greater than one IRS unit was jointly reviewed to reach consensus. The IRS scale table was moved to the Materials and Methods section to clarify the scoring procedure.

Statistical analysis

Data were analyzed using IBM SPSS Statistics version 25. Because IRS data were ordinal/semi-quantitative, ferritin expression scores were compared among groups using the Kruskal–Wallis test. When a significant overall difference was observed, pairwise comparisons were performed using Dunn's post hoc test with Bonferroni correction. A value of $p < 0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

Ferritin expression was successfully detected in ovarian granulosa cells in all experimental groups by immunohistochemical staining, as shown in Figure 2. Positive ferritin immunoreactivity was identified as brown cytoplasmic staining in granulosa cells. Ferritin expression was evaluated semi-quantitatively using the immunoreactive score (IRS), and the scoring criteria are presented in Table 1. Mean ranks are shown in Table 2.

The distribution of ferritin expression scores is illustrated in Figure 3. Ferritin expression showed a decreasing pattern across the nanocurcumin-treated groups, with the lowest scores observed in T3. This pattern was consistent with the mean rank values obtained from the Kruskal-Wallis analysis, in which the untreated endometriosis control group had the highest mean rank (23.00), followed by T1 (16.86) and T2 (12.43), whereas the lowest mean rank was observed in T3 (5.71). Overall statistical analysis using the Kruskal-Wallis test demonstrated a significant difference in ferritin expression among the four groups (H= 16.550, df= 3, p= 0.001), as shown in Table 3. Pairwise comparisons using Dunn-Bonferroni post hoc test are presented in Table 4. Only the T3 group differed significantly from the untreated endometriosis control group (adjusted $p < 0.001$). No statistically significant differences were observed between T3 and T2 (adjusted p= 0.756), T3 and T1 (adjusted p= 0.067), T2 and T1 (adjusted p= 1.000), T2 and control (adjusted p = 0.096), or T1 and control (adjusted p= 0.969). These findings indicate that nanocurcumin was associated with lower ferritin expression in ovarian granulosa cells, with the clearest and statistically supported effect observed at 10 mg/kg body weight.

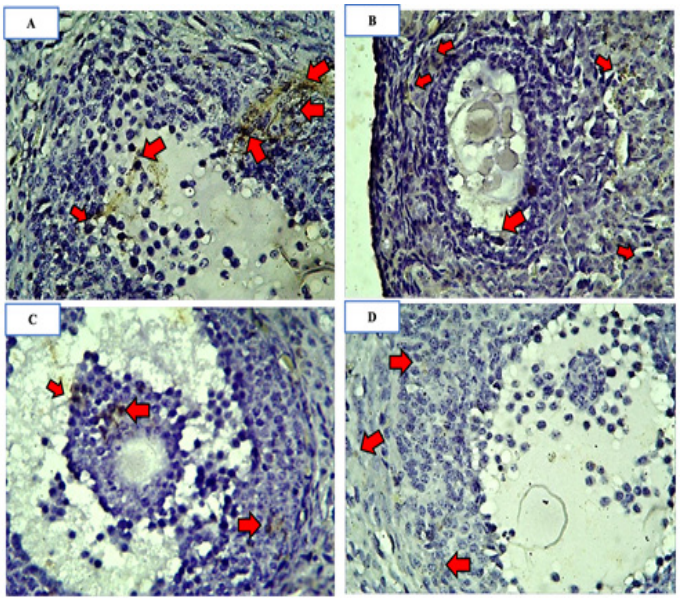

Figure 2: Immunohistochemical staining of ferritin expression in ovarian granulosa cells. Brown cytoplasmic staining indicates ferritin-positive granulosa cells. Ferritin immunoreactivity was strongest in the untreated endometriosis control group and weakest in the 10 mg/kg BW nanocurcumin group.

Table 1: The IRS semi-quantitative scale is the result of multiplying the positive cell percentage score (A) and the color reaction intensity score (B), IRS = (A × B).

A	B
Score 0: No positive cells	Score 0: No color reaction
Score 1: Positive cells <10%	Score 1: Low color intensity
Score 2: Positive cells 11-50%	Score 2: Medium color intensity
Score 3: Positive cells 51-80%	Score 3: High color intensity
Score 4: Positive cells more than 80%	

IRS=Immunoreactive score.

Table 2: Mean rank of ferritin expression in ovarian granulosa cells of endometriosis mice treated with different doses of nanocurcumin.

Group	N	Mean Rank
C (+)	7	23.00
T1	7	16.86
T2	7	12.43
T3	7	5.71

Table 3: Kruskal–Wallis test results for ferritin expression in ovarian granulosa cells.

Test statistics	Ferritin Score
Kruskal-Wallis H	16.550
df	3
Asymp. Sig.	0.001

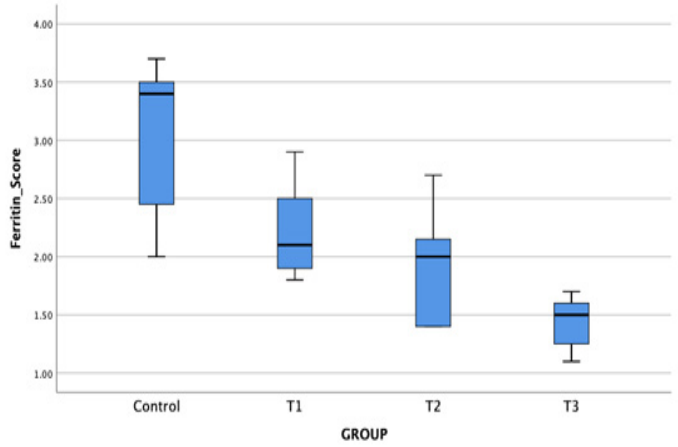

Figure 3: Semi-quantitative immunoreactive scores of ferritin expression. Ferritin expression was assessed using the immunoreactive score (IRS). The IRS distribution showed a decreasing pattern after nanocurcumin administration, with the lowest scores observed in the 10 mg/kg BW group.

Table 4: Pairwise comparisons of ferritin expression (IRS) in ovarian granulosa cells among experimental groups (Post Hoc Dunn–Bonferroni Test).

Comparison	Test statistic	Std. error	Std. test statistic	p value	Adjusted p-value[a]
T3-T2	6.714	4.387	1.530	0.126	0.756
T3-T1	11.143	4.387	2.540	0.011	0.067
T3-Control	17.286	4.387	3.940	0.000	0.000
T2-T1	4.429	4.387	1.009	0.313	1.000
T2-Control	10.571	4.387	2.410	0.016	0.096
T1-Control	6.143	4.387	1.400	0.161	0.969

Each row tests the null hypothesis that the Sample 1 and Sample 2 distributions are the same. Asymptotic significances (2-sided tests) are displayed. The significance level is .05. Significance values have been adjusted by the Bonferroni correction for multiple tests.

Endometriosis is increasingly recognized as a chronic inflammatory disorder characterized not only by estrogen dependence and persistent inflammation but also by dysregulated iron homeostasis (Giudice and Kao, 2004; Kobayashi *et al*., 2009). Recurrent cyclic bleeding from ectopic endometrial lesions promotes the accumulation of hemoglobin-derived iron within the peritoneal cavity and adjacent tissues, creating an iron-rich inflammatory microenvironment (Defrère *et al*., 2008). This excess iron contributes to oxidative stress and progressive tissue injury through iron-catalyzed redox reactions and reactive oxygen species generation, which further sustain inflammatory signaling and lesion persistence (Wyatt *et al*., 2023). Therefore, iron overload has become an important mechanistic link between endometriosis and reproductive dysfunction.

The ovary may be secondarily affected by endometriosis-associated iron dysregulation. Elevated iron concentrations have been reported not only in endometriotic lesions but also in ovarian tissue and follicular fluid, particularly in the presence of ovarian endometriomas (Sanchez *et al*., 2014; Patel *et al*., 2025). Granulosa cells are highly susceptible to this abnormal microenvironment because they are essential for follicular growth, steroidogenesis, and oocyte support. Iron overload in granulosa cells has been associated with oxidative stress, mitochondrial dysfunction, fibrosis, ferroptosis, and reduced follicular competence (Woo *et al*., 2020; Lin *et al*., 2020; Ni *et al*., 2022). Therefore, the stronger ferritin immunoreactivity observed in the untreated endometriosis group may reflect an adaptive cellular response to increased iron-related stress in ovarian granulosa cells.

Ferritin is the major intracellular iron-buffering protein that sequesters redox-active iron in a less toxic form. Increased ferritin expression is commonly interpreted as a protective cellular response to iron overload and oxidative stress (Wyatt *et al*., 2023). In the present study, higher ferritin expression in the untreated endometriosis group is consistent with the presence of an iron-rich oxidative microenvironment. Conversely, the reduction of ferritin expression after nanocurcumin treatment, particularly at 10 mg/kg body weight, suggests that nanocurcumin may have reduced the cellular stress that initially triggered ferritin upregulation. However, ferritin is an indirect marker and may also behave as an acute-phase reactant; therefore, reduced ferritin expression should not be interpreted as definitive evidence of reduced intracellular iron burden without direct measurements of iron status and oxidative stress.

The biological plausibility of this finding is supported by the known antioxidant, anti-inflammatory, and metal-chelating properties of curcumin (Aggarwal and

Harikumar, 2009; Hewlings and Kalman, 2017). Curcumin can interact with ferric ions through its β-diketone moiety, thereby potentially reducing intracellular labile iron pools and limiting iron-mediated oxidative damage (Borsari *et al*., 2002; Jiao *et al*., 2006). By decreasing redox-active iron availability and oxidative stress, curcumin may reduce the need for ferritin upregulation. The use of nanocurcumin in this study was intended to overcome the poor aqueous solubility and low bioavailability of conventional curcumin, allowing improved absorption and tissue delivery.

Although ferritin scores showed a decreasing pattern across the treatment groups, only the highest dose differed significantly from the untreated control after multiple-comparison correction. Therefore, the present findings support an association between high-dose nanocurcumin and lower ferritin expression, whereas evidence for a consistent graded dose-response across all tested doses remains limited. The numerical decrease observed in the lower-dose groups should be interpreted cautiously, as it may reflect biological variation and limited statistical power related to the relatively small sample size. Larger studies are required to confirm whether lower doses of nanocurcumin can produce statistically significant modulation of ferritin expression.

Recent mechanistic studies have further strengthened the relationship between iron overload and granulosa cell injury in endometriosis. Spatial transcriptomic and molecular analyses have shown that ovarian iron accumulation is associated with granulosa cell senescence, metabolic dysregulation, ferroptosis, and fibrosis (Li *et al*., 2025; Lin *et al*., 2020). These findings support the concept that the ovarian follicular microenvironment is a secondary target of endometriosis-associated iron toxicity. In this context, the reduction of ferritin expression following nanocurcumin administration may represent an early histological indication of decreased iron-related cellular stress within the ovary. Nevertheless, ferritin alone cannot fully define intracellular iron status or ferroptotic activity.

This study has several limitations. Ferritin expression was assessed only by immunohistochemistry, and additional biochemical or molecular parameters, such as labile iron concentration, malondialdehyde, glutathione peroxidase activity, ferroptosis-related proteins, and ovarian functional outcomes, were not measured. Therefore, the present results should be interpreted as evidence of altered ferritin immunoreactivity rather than direct confirmation that nanocurcumin attenuated intracellular iron overload or ferroptosis in ovarian granulosa cells. Future studies should integrate ferritin analysis with oxidative stress markers, ferroptosis-related pathways, and reproductive performance indicators to better clarify the mechanism by which nanocurcumin may protect ovarian function in endometriosis.

Overall, the findings of this study support the concept that iron-related stress is an important link between endometriosis and ovarian dysfunction. High-dose nanocurcumin was associated with lower ferritin immunoreactivity in ovarian granulosa cells, suggesting a potential modulatory effect on iron-related cellular stress. However, because ferritin is an indirect adaptive marker, further mechanistic studies are needed before firm conclusions can be drawn regarding intracellular iron burden, ferroptosis, or therapeutic relevance. In a broader context, this study may support future research relevant to SDG 3, particularly in the development of non-hormonal approaches to improve reproductive health in endometriosis.

CONCLUSION

Nanocurcumin was associated with reduced ferritin expression in ovarian granulosa cells in a murine model of endometriosis, with the clearest and statistically supported effect observed at 10 mg/kg body weight. Although reduced ferritin immunoreactivity may indicate modulation of iron-related cellular stress, additional molecular and functional analyses are required to confirm whether nanocurcumin directly affects intracellular iron burden, ferroptosis activity, and ovarian function.

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NOVELTY STATEMENT

This study provides experimental evidence that nanocurcumin administration is associated with altered ferritin immunoreactivity in ovarian granulosa cells in a murine model of endometriosis. The study adds to the emerging literature on iron-related ovarian changes in endometriosis by focusing specifically on granulosa-cell ferritin expression after nanocurcumin treatment. The strongest reduction was observed at 10 mg/kg body weight, supporting further mechanistic investigation in better-characterized experimental settings.

AUTHORS CONTRIBUTION

MYAW: Conceptualization, study design, experimental

work, data collection, statistical analysis, manuscript drafting. HH: Supervision, methodology validation, critical revision of the manuscript, interpretation of results. WW: Study supervision, experimental design guidance, data interpretation, manuscript review and final approval. All authors read and approved the final version of the manuscript.

Ethical approval

All procedures involving animals were conducted in accordance with institutional guidelines for the care and use of laboratory animals and were approved by the Ethics Committee of the Faculty of Veterinary Medicine, Universitas Airlangga, Surabaya, Indonesia (Approval No. KE.053.05.2022).

Generative AI and AI assisted technology statement

The authors declare that no generative AI and AI assisted technology was used in the creation of this manuscript.

Conflict of interest

The authors have declared no conflict of interest regarding the publication of this manuscript.

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