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N-acetylcysteine as an Investigational Molecular Modulator in Endometriosis: A Narrative Review

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ABSTRACT

Background: Endometriosis is an inflammatory condition featuring persistent oxidative stress. Usual hormonal therapy and surgery can be limited because they introduce contraceptive effects. *Aim:* This review considers the potential of N-acetylcysteine (NAC) as a candidate non-hormonal molecule that could influence endometriosis, while considering the preliminary and methodological weaknesses of the available data. *Materials and Methods:* A structured PubMed-MEDLINE search (January 2010 – May 2026) was performed to identify the role of N-acetylcysteine (NAC) in endometriosis. A comparative approach was used to summarize the methodological validity of preclinical animal studies and clinical trials and to assess study quality. *Results:* Evidence from mechanistic studies and experimental models indicates NAC as a candidate factor associated with molecular changes in tissue and lesion regression in preclinical models. Clinical research reports pain relief and a reduction in endometrioma size; however, the results are affected by small sample sizes, lack of randomization and placebo control, or mixed antioxidant formulations. *Conclusions:* Current knowledge is insufficient to support NAC as a conventional treatment for endometriosis. Limitations stemming from the heavy reliance on preclinical models and the confounding design of clinical trials hinder understanding of NAC's role. Further research needs to focus on randomized controlled trials on NAC alone. Showing the disease-modifying potential of NAC requires long-term outcomes.

Keywords: endometriosis, n-acetylcysteine (NAC), redox signaling modulation, proliferation-to-differentiation switch

1. INTRODUCTION

Background

Endometriosis represents an estrogen-dependent chronic illness characterized by the proliferation of endometrium-like lesions and/or stroma beyond the endometrium and myometrium (Tomassetti et al., 2021). The pathogenesis of this disease involves chronic inflammation, in which reactive oxygen species (ROS) production exceeds antioxidant defenses, leading to oxidative stress (Clower et al.,

2022). Endometriosis occurs in women of reproductive age all around the world, with a prevalence rate of around 10%. It is known to impact health through symptoms of chronic pelvic pain, dysmenorrhea, dyspareunia, dyschezia, dysuria, and infertility (Zondervan et al., 2020). This pathology negatively impacts psychological health and is associated with disruption of the education and employment opportunities (Facchin et al., 2026).

Current Clinical Guidelines and Standard of Care

At the moment, endometriosis cannot be completely cured (As-Sanie et al., 2025). Treatment strategy includes symptom control and the prevention of recurrence. According to the ESHRE guidelines of 2022, a combination of hormonal contraceptives is recommended for managing pain, while progestins act as second-line medications for controlling pain and promoting fertility. GnRH agonists and antagonists should be used after other treatment options fail. Another treatment pillar involves surgery with a predilection towards lesions excision and cystectomy, with post-surgical hormone suppression being necessary unless pregnancy is sought by a woman (Becker et al., 2022). It is essential to emphasize that N-acetylcysteine (NAC) described in the current review is not a part of any treatment protocol and is not recommended as for now.

Unmet Medical Need and Treatment Gap

A serious problem associated with the majority of currently available hormonal treatment options is the fact that the mechanism behind these medicines consists of blocking ovulation. As a consequence, these methods are contraception methods and cannot be administered to those women who wish to conceive (Taylor et al., 2021). The recurrence rate is high when a patient does not receive hormone suppression after surgery (Veth et al., 2024). Moreover, some surgical approaches have been shown to deplete ovarian reserve (Li et al., 2026). Thus, a medical gap arises due to the necessity of non-hormonal drug development that will stop disease progression while not affecting reproductive capabilities.

Research Objective

The current narrative review evaluates the potential of N-acetylcysteine (NAC) as a model for experimental research into the molecular regulation of endometriosis. Specifically, the aim of the present research aims to discuss the opportunities for developing a non-hormonal model that facilitates stabilization of the disease progression without affecting hormones. At the same time, given that the majority of scientific work addressing the problem in question consists of *in vitro* and preclinical research, this review focuses on this important issue.

2. REVIEW METHODS

Search Strategy

To get a picture of how NAC could affect endometriosis, a thorough review of the PubMed/MEDLINE database was performed. The timeline for the literature search was set from January 2010 to May 2026. The process relied on a combination of Medical Subject Headings (MeSH) terms: (“endometriosis” OR “endometrioma”) AND (“N-acetylcysteine” OR “NAC” OR “N-Acetyl cysteine”).

Selection Criteria

The inclusion criteria targeted research analyzing NAC as an intervention in the endometriosis model system or as an important factor to be considered in studies involving the disease. As a consequence of a gap in current therapies, parameters of interest included oxidative environmental changes, alterations in lesion size, pain scores, and reproductive performance. Studies investigating monotherapy were chosen to isolate the modulatory effect of NAC directly; however, multicomponent antioxidative studies were included as well to examine the antioxidative capabilities of the compound. During the initial screening stage, reviews and meta-analyses were excluded. During the eligibility assessment, papers related to other pathologies, treatments, hormonal manipulations, and other unrelated matters were excluded, resulting in the selection of 14 papers for the review. For presentation purposes and to ensure methodological transparency, a PRISMA flowchart was created (Figure 1).

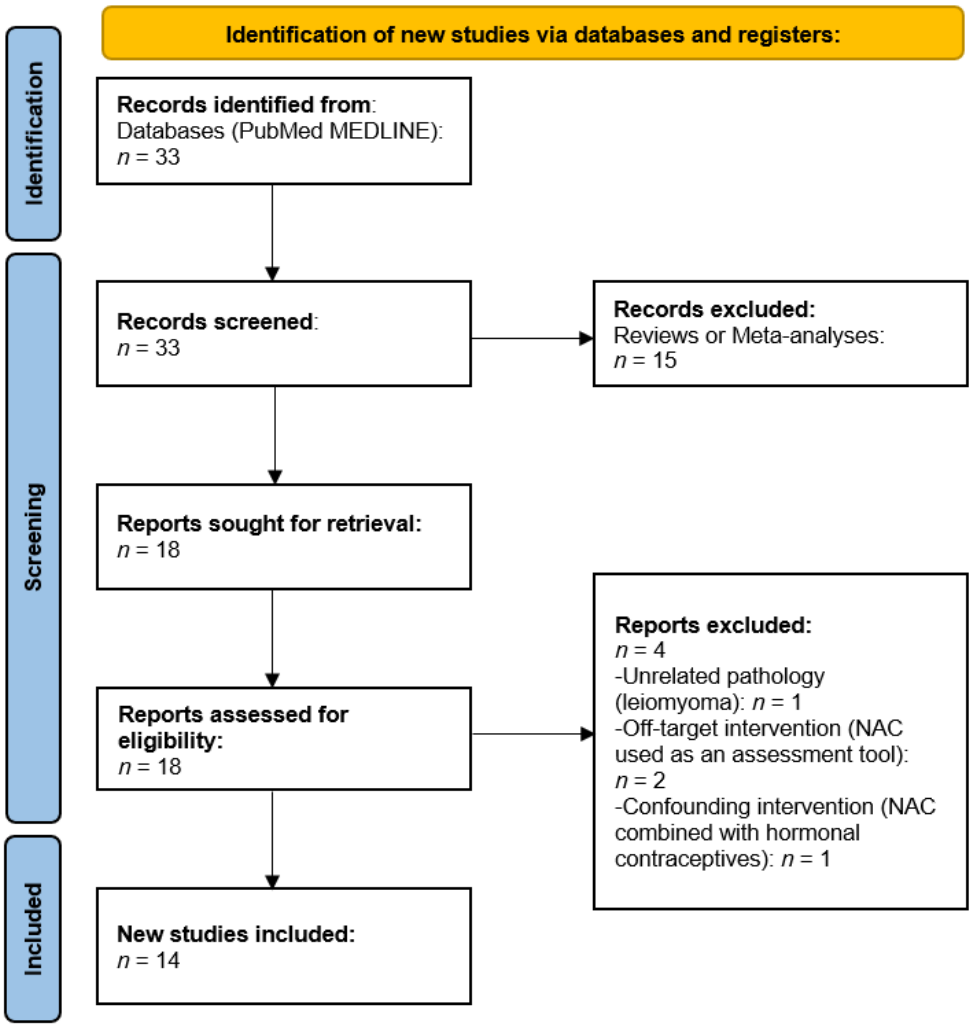

Figure 1. PRISMA flow chart

Data Extraction and Synthesis

Narrative synthesis was applied. Given the exploratory character of current research and the heterogeneity of approaches used in relevant papers, a critical analysis of methodology was conducted for each study. The synthesis focused on quality, methodological aspects, and risk of bias in preclinical models and clinical trials to isolate NAC's molecular efficacy.

3. RESULTS

Study Findings: Murine Model

A possible "proliferation-to-differentiation switch" mechanism was first tested in a group of 40 mice, in which NAC administration reduced endometrioma mass by 60% compared with untreated controls. The regression was observed due to the antiproliferative effect, characterized by a decrease in the proliferation marker Ki-67, from 1.88±0.28% in the untreated animals to 0.87±0.11% ($P < 0.01$). It seems that NAC induced differentiation and maturation processes, as reflected by E-cadherin localization at cell junctions rather than in the cytoplasm, with a 67% increase in the junctional protein compared with controls. This effect corresponded to the lower motility and invasiveness of the endometriotic cells. Moreover, the treatment reduced cyclooxygenase-2 (*Cox2*) mRNA expression and inhibited matrix metalloproteinase-9 (MMP-9) activity by more than 60%. Thus, NAC targets inflammation and invasive processes characteristic of this pathology. The described findings provide the basis for this mechanism, but they are still only the first stage of experimental studies, since it is necessary to account for the specific microenvironment of human organisms when translating findings from animal experiments into practice (Pittaluga et al., 2010).

Clinical Observations: Results in Non-Randomized Populations

The efficacy of N-acetylcysteine (NAC) therapy in the clinical practice of endometriosis among 92 patients, 47 treated and 45 controls without the drug administration, has been evaluated using ultrasound diagnosis of endometriomas. To optimize pharmacokinetics, a "pulse therapy" was utilized: NAC was given three times per day at 600 mg, resulting in an overall intake of 1.8 g/day for three days a week, followed by a four-day medication-free period. During three months of observations, a minimal 1.5 mm reduction in cyst size in treated patients was observed, compared with a 6.6 mm increase in untreated patients ($P = 0.001$). While the discussed study is useful to transfer the findings from laboratory animals to the clinical setting, its methodology bears certain restrictions due to the relatively low number of patients ($n = 92$) involved in the research process, as well as due to the rather brief observation period (3 months), which is not sufficient to determine the durability of the effects observed. The investigation reported 24 operations canceled because of symptom remission: dysmenorrhea (55%, $P = 0.001$), dyspareunia (50%, $P = 0.027$), and chronic pelvic pain (59%, $P = 0.015$). Without a placebo control, it is impossible to distinguish the drug's physiological effect from placebo-related changes in subjective complaints.

A morphologically differentiated epithelium and higher expression levels of junctional proteins like E-cadherin and β-catenin have been identified in treated lesions. A simultaneous decrease in the *COX-2* expression has also been established. It could explain cyst regression via the hypothesized mechanism, which includes lower Prostaglandin-E2 (PGE2) production, thereby decreasing the stimulation of aromatase activity and estrogen formation. The immunohistochemical approach to confirm the identified biochemical mechanisms has been carried out by the authors on 4 cyst samples taken from the operated patients (laparoscopy) to avoid possible confounding factors. The described research findings are prone to selection bias, since the assignment of patients to the control and treatment groups depended on their willingness to undergo NAC administration. In addition, the study's one-site design limits its external validity (Porpora et al., 2013).

Symptom Evaluation: Prospective Single-Arm Data

Prospective research involving 120 female subjects demonstrated the clinical efficacy of the 3-day NAC pulse therapy protocol. It was reported that there was a decrease in physical lesions, as the mean cyst diameter went down from 36.5 ± 25.4 mm to 33.0 ± 23.5 mm during three months ($P < 0.001$). Nevertheless, given the significant Standard Deviation and the lack of a control group, one can see the preliminary nature of the results. The number of patients involved in the research does not represent an adequate sample size considering the widespread occurrence and different types of the disease. The period of three months seems to be too short to evaluate the long-term effects of such a chronic and recurrent disorder. Concurrent changes include both lowering serum cancer antigen (CA125) (45.5 U/mL to 35.6 U/mL; $P = 0.001$) and body mass index (BMI) of the participants (22.2 to 21.2 kg/m^2). Those changes seem to reflect the anti-inflammatory properties of NAC rather than lesion-specific effects and cannot be attributed solely to the drug.

Management of clinical symptoms has resulted in lower Visual Analog Scale (VAS) scores for dysmenorrhea (6.9 to 4.8; $P < 0.0001$) and chronic pelvic pain (7.2 to 5.7; $P < 0.001$), as well as decreased need for NSAID usage. A single-arm design does not allow evaluation of the intervention's efficacy relative to the control group, making the conclusions questionable. In addition, there is a high level of uncertainty related to reproduction outcomes, as only 39 out of 52 patients conceived spontaneously within six months. Since the researchers have noted a decrease in dyspareunia, it is quite challenging to differentiate between cellular receptiveness and behavioral changes, as increased sexual activity might have been the consequence of less pain. Therefore, biological efficacy requires verification in future RCTs (Anastasi et al., 2023).

IFN-γ Synergy and Programmed Organelle Failure: *In Vitro* Mechanisms

An *in vitro* approach aimed at elucidating the molecular mechanisms underlying the proposed molecular switch, using human endometriotic (*12Z*) and endometrial (*HESC*) stromal cell lines. Consequently, these outcomes cannot be translated clinically and require validation in human-derived tissue. Therefore, the results of this work can only be validated clinically for human tissue samples and cannot yet be applied clinically. This research revealed that NAC's activity is dependent on the immune milieu, demonstrating a cooperative effect with Interferon-gamma (IFN-γ) in inhibiting cell proliferation. While they each inhibited cell proliferation, their combination led to the production of antiproliferative effects by inducing mitochondrial dysfunction and ER stress, as evidenced by elevated levels of p-IRE1-α. A combined analysis strategy, comprising xCELLigence (real-time cell impedance analyses) assays, flow cytometry, immunofluorescence staining, western blotting, and metabolomics analysis, gave a detailed understanding of the molecular processes driving this disturbance of energy pathways in cells.

The data revealed that it leads to cell starvation and organellar dysfunction, where p-IRE1-α acts as a mediator of this process, which makes it a possible therapeutic or prognostic target. Despite these advances, this study was limited by the use of immortalized cell lines, such as *12Z* and *HESC*, which exhibit characteristics similar to cancerous cells and may therefore lead to increased metabolic changes. Additionally, NAC did not exert any effects on cytokine-induced cell proliferation, like IL-6, or TNF-α, showing that its therapeutic utility may be limited to specific inflammatory profiles rather than serving as a universal intervention (Karakoç et al., 2025).

Systemic Immunomodulation and Regression of Endometriotic Lesions

The *in vivo* efficacy of systemic N-acetylcysteine (NAC) was compared with current pharmaceutical options in a randomized experiment in rats using surgically induced endometriosis. The findings indicated that NAC administration after 3 weeks reduced the average size of endometrial ectopic lesions (61.2±57.9 mm^2 to 30.5±21.9 mm^2; P = 0.043). While this treatment showed competitive performance to leuprolide acetate, causing a reduction in lesion size (44.3±43.5 mm^2 to 19.6±20.0 mm^2; P = 0,008) as well as amifostine (30.8±16.4 mm^2 to 18.7±15 mm^2; P = 0.012), no changes were observed in the control group. Apart from lesion structural diminishment, a decrease in levels of TNF-α was detected both in systemic (41.7±9.9 pg/mL to 17.25±10.1 pg/mL; P = 0.01) and peritoneal fluid (37.5±15.3 pg/mL to 19.2±13.1 pg/mL; P = 0.06) within NAC-, amifostine- and leuprolide-treated groups. Although this experiment exhibited promising results, there are limitations to its generalizability. First, rodents with surgically induced endometriosis do not replicate the complex immune pathology seen in humans, and second, since the treatment lasted only three weeks, there is a probability of endometriosis recurrence, or withdrawal of improvements in chronic clinical signs of pelvic pain and infertility (Onalan et al., 2014).

Modulation of Autophagy in Endometriotic Lesions

Another piece of literature shows that N-acetylcysteine (NAC) regulates defective autophagy in ectopic endometrium via inhibiting reactive oxygen species (ROS). Using a surgically induced rat model (n = 40), investigators discovered that the endometriosis-associated inflammatory and oxidative environment elevates ROS, which stimulates the expression of certain autophagy proteins, such as microtubule-associated protein light chain 3 (LC3), and Beclin-1. Injection of the peritoneum with NAC (200 mg/kg) for 21 days reduced oxidative stress and subsequently inhibited both LC3 fluorescence and Beclin-1 protein expression. This effect of NAC is related to interference with the connection between ROS and autophagy. It helps avoid ongoing oxidative damage and supports cell survival strategies, thereby leading to lesion proliferation. However, the use of the surgically induced rat model is limited by its lack of translational potential, because suturing uterine tissue cannot repeat the multifactorial pathogenesis of endometriosis in humans. Additionally, the small number of animals per subgroup (n = 10) shows variability, and the relatively short treatment period makes it challenging to extrapolate results (Lu et al., 2020).

3D Spheroid Modeling and Glutathione Exhaustion under NAC Interventions

Modern *in vitro* studies have moved to 3D modeling to more accurately simulate metabolic stress. As part of this research, 3D tissue-like models were created from biopsies of human endometriosis lesions, *12Z* cells, and Ishikawa cells as the control culture. They underwent an oxidative challenge with a low concentration of hydrogen peroxide (H_2O_2) to assess the limitations of pure NAC therapy. According to the findings, ectopic *12Z* tissue is prone to redox-induced stress; thus, its total intracellular glutathione content decreased by 72% under acute oxidative conditions. When used as a molecular modulator, NAC hindered lipid peroxidation and reduced malondialdehyde (MDA) levels, which had increased threefold, back to baseline. Additionally, cytoplasmic proteins were resistant to oxidation due to NAC intervention; hence, there was no protein carbonylation in the test group, whereas there was a fourfold increase in protein carbonyl content. On the other hand, NAC could not reverse oxidative DNA fragmentation and genomic damage. Such a limitation implies that iron-dependent DNA damage caused by endometrial hemorrhage cannot be targeted by a conventional radical scavenger such as NAC and that it occurs through alternative biochemical pathways.

As for these models, although tissue viability is preserved, they can only be considered complete once metabolic manipulations beyond antioxidant monotherapy are undertaken. From the methodological point of view, major limitations should be considered. For example, *in vitro* testing uses immortalized cell lines rather than primary human tissues, which cannot imitate all aspects of the physiological processes occurring in living endometriotic tissue *in vivo*. Another limitation includes the use of cancerous Ishikawa cells to model oxidative conditions. Finally, it should be pointed out that iron-driven biochemical reactions resulting from erythrocyte hemolysis in human endometriomas are not accounted for in this traditional model (Coelho et al., 2026).

NAC in Multicomponent Supplementation

While the individual effects of NAC are the primary topic of the review at hand, the complexity of endometriosis is reflected by studies exploring multicomponent antioxidant supplementation. Research done with mouse models and endometriotic endothelial cells demonstrates the ability of the three-component preparation containing NAC, alpha-lipoic acid, and bromelain to function as a molecular modulator influencing the activity of endometriotic cells in specific ways. Together, this mixture brings about an increase in programmed cell death through caspase-3 and -7 activation and the downregulation of inflammatory factors such as VCAM-1 in lesion-derived endometriotic cells, without affecting normal myometrial/uterine cells.

Clinical trials confirm these results with a decrease in cyst size and fewer cysts seen in the treated patients. Nonetheless, this conclusion is based on the impact of the entire multicomponent formula rather than that of NAC only. There are some limitations of the *in vivo* study to be noted here. For one, SCID mice were used for experiments, which means that their adaptive immune system is compromised and does not fully represent the interaction between inflammation and other factors that are present in human endometriosis. In addition, a 21-day-long intervention period cannot serve as an approximation for the multiyear-long development of the disease, which is why cyst prevention cannot be confirmed (Agostinis et al., 2015).

In the case of a multicenter clinical study conducted on the basis of the LEAP trial, a cohort of 346 female patients with endometriosis-related pelvic pain was investigated, where the subset included 45 women interested in pregnancy and not taking any hormonal medications. During a six-month follow-up protocol, the analysis showed decreased levels of pain scores according to VAS (6.66 ±1.81 to 3.14 ±2.22; $P < 0.001$). The study also showed significant changes associated with a decrease in the number of patients having high pain index values (from 40.2% at baseline to 3.6% at study conclusion; $P < 0.001$). In addition, the frequency of consumption of standard analgesics was reduced, as the need for rescue NSAID became lower (86.4% to 37.4%; $P < 0,001$). From the standpoint of methodology, as applicable for this review, it should be highlighted that the LEAP trial did not involve only the NAC medication as a monotherapy. Instead, participants received the mixture containing the NAC dose of 600 mg per day with 200 mg of alpha-lipoic acid (LA), 25 mg of bromelain (Br), and 10 mg of zinc. Even though the data about 27 cases of spontaneous pregnancies shows potential for fertility enhancement in combination with pain control, the design of the experiment does not allow us to prove any therapeutic effects of NAC specifically (Lete et al., 2018).

Other research focused on evaluating the synergism between NAC and natural polyphenolic agents (curcumin and quercetin). In a twofold approach, scientists used both the *in vitro* model based on endometrial cell cultures and the *in vivo* model involving 33 female subjects diagnosed with endometriosis. Treatment with antioxidants in the combined form during 60 days contributed toward improved pain indices, including reduction in dysmenorrhea (Numeric Rating Scale NRS 6.1 to 2.8; $P < 0.01$), chronic pelvic pain (NRS 5.7 to 2.1; $P < 0.01$), and dyspareunia (NRS 5.3 to 2.5; $P < 0.01$) and less consumption of NSAIDs. However, the use of the mixture still hinders the isolation of the impact of NAC treatment. Moreover, the small sample size limits further generalization due to limited information on recurrence over several months (Fadin et al., 2020). Overall, these experiments confound existing evidence because NAC cannot be identified as the factor responsible for the beneficial effects.

Follicular Redox Modulation

In addition to modulating redox activity in endometriotic tissue, more comprehensive molecular effects have been studied in reproductive tissues. As has been shown, NAC promotes the nuclear translocation of nuclear factor erythroid 2-related factor 2 (Nrf2), thereby triggering the transcription of several antioxidant enzymes in mouse oocytes (Fan et al., 2022). NAC was used to assess its effects on embryonic development and meiotic spindle integrity in oocytes from cows incubated with follicular fluid from patients with mild endometriosis characterized by increased oxidative stress (Giorgi et al., 2016; 2021). Nevertheless, these data warrant detailed consideration, as oxidative stress is likely a downstream effect of the main pathogenesis of endometriosis (hormonal). The external validity of these studies is poor; therefore, they can be interpreted only as explorations, as there is still insufficient evidence for clinical use. As mentioned above, NAC is considered as an intervention for improving oocyte quality. Therefore, a double-blind RCT of 25 infertile women with stage III/IV endometriosis was conducted to explore this issue further. In the absence of statistical significance, these clinical results must be interpreted as preliminary given the small sample size. The study showed an improvement in Total Antioxidant Capacity (TAC) upon administration of 1200 mg/day of NAC for six weeks ($P = 0.031$). Moreover, cellular analysis of GCs confirmed a defensive mechanism through downregulation of *BAX* and *CASP-3*, responsible for apoptosis, and upregulation of *BCL2* ($P < 0.05$). There was also a lower percentage of defunct oocytes (4.9%) versus the placebo group (6.1%). Although this study provides

an approach to exploring the redox-mediated oocyte protection mechanism, there is insufficient evidence for this biological shift, as the sample size of 25 participants is too small (Heshmati et al., 2026).

4. DISCUSSION

The literature on NAC in endometriosis varies, ranging from experimental laboratory data to clinical research. The research on *in vitro* models has reported interesting NAC's coaction with IFN-γ, involving stress-related organelle signaling (Karakoç et al., 2025). However, experimental works have certain limitations. More precisely, most experiments use immortalized *12Z* and *HESC* cell lines, together with cancer-like control cells that cannot imitate complicated, inflammatory conditions typical of the pelvic area and do not involve iron metabolism pathways (Karakoç et al., 2025; Coelho et al., 2026). This limits their external validity and ability to replicate chronic and progressive features inherent to human endometriosis.

Preclinical animal studies involving rodents have shown both lesion regression and decreased cytokine levels. Although the results may seem positive, they cannot be generalized to clinical benefits due to the use of surgically induced implants, an acute form of damage rather than a progressive inflammation that defines endometriosis. These studies also use a small subgroup, a very short time of drug administration, and no specific human clinical outcomes, making it difficult to infer the possible durable effectiveness or safety of the therapy (Pittaluga et al., 2010; Onalan et al., 2014; Lu et al., 2020; Agostinis et al., 2015).

Clinical evidence gathered via observational studies, as well as prospective trials involving single-arm analyses and multicenter studies, faces additional challenges because NAC is often included in multi-component drugs containing LA, Br, and zinc. Multiple substances make it impossible to identify the actual effects of NAC, hence limiting the possibility of attributing beneficial effects observed in patients to it (Agostinis et al., 2015; Lete et al., 2018; Fadin et al., 2020). Moreover, the research on this topic features many limitations in methodology, like the use of non-randomized study designs, a lack of placebo controls, insufficient numbers of participants, and very limited follow-ups, which do not allow the assessment of lesion regression, alleviation of pain or any other reported change in the long term (Porpora et al., 2013; Anastasi et al., 2023).

Overall, the current state of knowledge, ranging from cellular processes to clinical findings in humans, remains highly exploratory. The reliance on artificially created cells, experimentally operated animals, and unclear multi-component compositions in clinical settings precludes establishing NAC as the standard. To make the comparison more transparent, a table 1 has been provided. In addition, the exploratory nature of the findings is evident in reproductive research. While animal experiments suggest benefits of NAC on egg quality, human tissue samples were not used in this case (Fan et al., 2022; Giorgi et al., 2016; 2021). Pilot human trials in this area have suffered from low power and a lack of clear results (Heshmati et al. 2026).

Table 1. Overview of preclinical and clinical studies investigating NAC in endometriosis.

Author	Study design	Sample size	Intervention	Main Outcomes	Principal Limitations
Pittaluga et al., 2010	Experimental murine study	n = 40 mice	NAC oral administration vs. untreated controls	60% reduction in lesion mass; Ki-67 decrease (52% to 23%); repositioning of junctional E-cadherin; downregulation of *Cox2* and MMP-9.	Animal model: limited translational relevance to human tissue.
Porpora et al., 2013	Single-center observational cohort	n = 92 women (47 NAC-treated; and 45 control group)	NAC oral "pulse therapy" (1.8 g/day, 3 days/week) for 3 months	Mean cyst reduction of 1.5 mm (vs 6.6 mm increase in controls P = 0.001); relief in dysmenorrhea (55%, P = 0.001), dyspareunia (50%, P = 0.027), chronic pelvic pain (59%, P = 0.015).	Non-randomized design; single-center design: limited external validity; small cohort; short follow-up period; lack of placebo control.
Anastasi et al.,	Prospective	n = 120	NAC oral "pulse	Reduction in VAS score:	Non-randomized,

2023	single-arm cohort	women	therapy" (1.8 g/day, 3 days/week) for 3 months	dysmenorrhea (6.9 to 4.8; $P < 0.0001$), chronic pelvic pain (7.2 to 5.7; $P < 0.001$); decrease in cyst size (36.5 to 33.0 mm, $P < 0.001$); reported spontaneous pregnancies.	single-arm design: absence of control group; small cohort; brief follow-up period; incoherence in metabolic shifts (BMI); behavioral confounding of reproductive data.
Karakoç et al., 2025	*In vitro* experimental study	Human cell lines (*12Z*/ *HESC*)	Addition to culture medium (NAC combined with IFN-γ)	Synergistic induction of mitochondrial dysfunction and ER stress via p-IRE1-α; suppression of energy pathways causing cellular starvation.	Modeling gap using immortalized cell lines: exaggerated metabolic shifts; ineffective against IL-6 or TNF-α driven proliferation.
Onalan et al., 2014	Experimental *in vivo* animal study	$n = 40$ female rats	NAC vs. Leuprolide acetate and amifostine	Macroscopic regression of endometriotic implant surface area (61.2±57.9 mm^2 to 30.5±21.9 mm^2; $P = 0.043$); decrease in TNF-α systemic (41.7±9.9 pg/ml to 17.25±10.1 pg/ml; $P = 0.01$) and local peritoneal fluid (37.5± 15.3 pg/ml to 19.2±13.1 pg/ml; P =0.06).	Surgically induced model does not replicate spontaneous human disease pathogenesis; acute 3-week treatment limits long-term relevance; lacks human clinical endpoints.
Lu et al., 2020	Experimental *in vivo* animal study	$n = 50$ female rats	NAC (21 days) vs. Catalase and Control	Reduced Local ROS levels; downregulated autophagy markers (LC3 and Beclin-1) in ectopic lesions.	Surgically induced animal model does not mimic human pathogenesis; small sample size per subgroup.
Coelho et al., 2026	*In vitro* 2D and 3D spheroid experimental study	Human cell lines (*12Z* vs. Ishikawa)	Pretreatment with isolated NAC (5mM in 2D / 1.25mM in 3D) prior to controlled H_2O_2 oxidative challenge	NAC restored cell viability and prevented lipid peroxidation and protein carbonylation; 3D modeling captured a 72% depletion of the total glutathione pool; NAC failed to mitigate oxidative DNA fragmentation.	Low external validity: *in vitro* architecture using immortalized cells lacking multicellular and inflammatory complexity of *in vivo* lesions; adenocarcinoma origin of the comparator line introduces cancer-specific redox adaptations; lacks iron-driven pathways.

Agostinis et al., 2015	Experimental *in vitro* / *in vivo* murine study	*n* = 16 SCID mice and human endothelial cell lines (EECs/UtMECs)	Oral administration of combined mixture (NAC 250 m + LA 125 mg + Br 12.5 mg / day) vs. untreated controls	Lower number and smaller size of cysts *in vivo*; synergistic downregulation of VCAM-1 expression in EECs; selective induction of apoptosis via caspases 3 and 7 activation.	Low external validity: preclinical animal model using SCID mice lacking functional adaptive immunity; extremely brief 21-day intervention timeframe; therapeutic success depends on multi-ingredient synergy.
Lete et al., 2018	Multicenter, open-label, non-comparative clinical trial	*n* = 346 women	Oral intake of a combination tablet containing 600 mg NAC, 200 mg LA, 25 mg Br, 10 mg Zinc/day for 6 months	Significant drop in mean VAS scores (6.66 to 3.14; $P < 0.001$); a reduction in the proportion of patients suffering from severe pain (40.2% to 3.6%; $P < 0.001$); reduction in rescue NSAIDs reliance from 86.4% to 37.4% ($P < 0.001$); 27 spontaneous pregnancies.	Open-label, non-comparative trial; architecture lacking placebo control arm; low specificity: fixed multicomponent formulation makes it impossible to isolate or verify the therapeutic effect of the NAC module.
Fadin et al., 2020	Experimental *in vitro* and *in vivo* medical trial	*In vitro* (β-estradiol-induced endometrial cells) and *n* = 33 women	NAC+ Tumeric + Quercetin for 60 days	*In vitro:* Downregulated pro-inflammatory cytokines (IL-6, TNF-α) and induced apoptosis. *In vivo*: Reduced dysmenorrhea (NRS 6.1 to 2.8; $P < 0.01$), chronic pelvic pain (NRS 5.7 to2.1; $P < 0.01$) and dyspareunia (NRS 5.3 to 2.5; $P < 0.01$) as well as a decrease in NSAID reliance.	Small sample size; short follow-up duration; lack of a randomized placebo control group; low specificity: the isolation of NAC's effect is not possible

5. CONCLUSION

Despite the present research on NAC in the context of endometriosis, the existing translational gap cannot be ignored, with a simple experimentation design being used and clinical research being structurally invalid. It uses immortalized cells *in vitro* as well as animals that underwent surgery to create similar conditions. Most importantly, the existing data from clinical experiments are compromised by the simultaneous use of several components of treatment. Observational studies, in addition, suffer from relatively small sample sizes, a lack of randomization, and inadequate follow-up. The placebo effect can easily influence the results of such studies, leading to high bias. The only solution here would be to move on to conducting RCTs in which NAC is used as the sole intervention.

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Informed consent

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Ethical approval

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Conflict of interest

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Data and materials availability

All data associated with this study will be available based on the reasonable request to corresponding author.

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