

Innovative Approach to Endometriosis: Nanotechnology

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Abstract

Endometriosis affects an estimated 190 million women of reproductive age globally, highlighting the urgent need for innovative treatment options due to the limitations of current therapies and diagnostic methods. This study explores the potential of nanotechnology in revolutionizing endometriosis treatment through the comparison of silicon naphthalocyanine (SiNc) and kinase insert domain receptor magnetic nanoparticles (KDR-MN). A retrospective analysis was conducted on these nanotechnologies, focusing on their effectiveness in imaging and thermal ablation of endometriotic lesions. Characterization of nanoparticles was performed using transmission electron microscopy (TEM) and dynamic light scattering (DLS), while fluorescence microscopy assessed nanoparticle uptake in endometriotic cell lines. The therapeutic efficacy of thermal ablation was evaluated using an alternating magnetic field (AMF) and laser system. In vivo studies involved adult rhesus macaques with advanced endometriosis, with biopsies implanted into SCID mice. Results indicated that SiNc could serve as a single-agent nanopatform for photothermal therapy (PTT) and near-infrared (NIR) fluorescence imaging, effectively demarcating lesions and achieving complete eradication within four days' post-treatment. KDR-MN demonstrated targeted delivery to endometriotic tissues, producing significant negative contrast on MRI and effective thermal destruction at elevated temperatures. Both SiNc and KDR-MN show promising potential for efficient imaging and thermal ablation of endometriotic lesions, underscoring the innovative application of nanotechnology in enhancing endometriosis management. These findings pave the way for future research into targeted therapies that improve treatment outcomes for affected women.

Keywords: *Endometriosis, Nanotechnology, Silicon Naphthocyanine (SiNc), KDR-MN, Thermal ablation*

Introduction

Endometriosis is a complex and often debilitating condition characterized by the presence of endometrial-like tissue outside the uterus, leading to chronic pain, infertility, and a range of other symptoms that significantly impact the quality of life for those affected [14]. It is estimated that approximately 10% of reproductive-age women suffer from this disease, yet it remains underdiagnosed and misunderstood. Traditional methods of diagnosis primarily rely on invasive laparoscopic surgery, which can delay treatment and exacerbate patient suffering. Current treatment options, including hormonal therapies and pain management strategies, often provide only temporary relief and may not address the underlying pathology of the disease.

Given the limitations of conventional diagnostic and therapeutic approaches, there is an urgent need for innovative solutions that can enhance early detection and provide more effective treatment modalities. This is where nanotechnology emerges as a promising frontier in the fight against endometriosis. Nanotechnology involves manipulating matter at the nanoscale—typically between 1 to 100 nanometres—to create materials with unique properties that can be harnessed for medical applications. The small size of nanoparticles allows them to interact with biological systems in ways that larger particles cannot, enabling targeted delivery and enhanced efficacy.

One of the most significant advantages of nanoparticles in the context of endometriosis is their potential for targeted drug delivery. Traditional systemic therapies often result in widespread distribution throughout the body, leading to side effects that can diminish patient compliance. In contrast, nanoparticles can be engineered to deliver therapeutic agents directly to endometriotic lesions while sparing healthy tissues. This targeted approach not only enhances the effectiveness of treatments but also minimizes adverse effects, providing patients with a more tolerable therapeutic experience.

Moreover, nanoparticles can be designed to respond to specific stimuli within the body—such as pH changes or enzymatic activity—allowing for controlled release of drugs precisely at the site of action [3][4]. This capability could revolutionize how we manage pain associated with endometriosis by providing sustained relief without continuous dosing or high systemic concentrations.

In addition to their role in drug delivery, nanoparticles hold promise for improving diagnostic techniques. Advanced imaging modalities utilizing nanoparticle contrast agents can enhance the visualization of endometrial lesions during non-invasive imaging procedures

such as magnetic resonance imaging (MRI) or ultrasound [10]. By improving the sensitivity and specificity of these imaging techniques, nanoparticles could facilitate earlier diagnosis and intervention, ultimately leading to better patient outcomes.

As we explore this innovative approach to endometriosis management, it becomes clear that integrating nanotechnology into clinical practice could not only transform patient outcomes but also pave the way for a deeper understanding of this enigmatic disease. The potential applications of nanoparticles in both diagnosis and treatment underscore a paradigm shift in how we approach endometriosis—moving from traditional methods toward a more personalized and effective strategy that addresses both the symptoms and root causes of this challenging condition. Through continued research and development in nanotechnology, we stand on the brink of a new era in endometriosis care that promises improved quality of life for countless women worldwide.

Current Methods of Diagnosis of endometriosis

Method	Description	Advantages	Disadvantages
Clinical evaluation	Assessment of medical history and symptoms	Non-invasive, cost-effective	Subjective; cannot confirm diagnosis
Pelvic examination	Physical examination to check for abnormalities	Quick, non-invasive	Limited sensitivity; may miss internal lesions
Ultrasound	Imaging technique using sound waves to visualize reproductive organs	Non-invasive, widely available	Limited detection capability; operator-dependent
MRI	Imaging technique using magnetic fields for detailed internal images	High sensitivity/specificity for deep lesions	More expensive; requires specialized equipment
Laparoscopy	Surgical procedure allowing direct visualization and treatment	Definitive diagnosis/treatment	Invasive; requires anaesthesia

Table 1. This table represents the methods of diagnosis of endometriosis which is currently being used around the world, it elaborates the advantages and disadvantages of the methods. Among the above mentioned methods laparoscopy is considered the most accurate method for diagnosing endometriosis due to its ability to provide direct visualization of lesions. It

allows for confirmation through biopsy if necessary and can also facilitate immediate treatment.

Diagnosis of Endometriosis - Country wise	Gold standard	Additional methods
India	Laparoscopy	Clinical history Clinical examination Ultrasonography MRI
New Zealand	Laparoscopy	Ultrasonography MRI
Russia	Laparoscopy	Based on anamnesis Ultrasonography MRI Histological examination of excised tissue
China	Laparoscopy	Doppler ultrasound MRI CT scan
Malaysia	Laparoscopy	Pelvic exam Ultrasonography
USA	Laparoscopy	Pelvic exam Ultrasound MRI

Table 2. Here is representation of the current methods of diagnosis of endometriosis used in India, New Zealand, Russia, China, Malaysia and USA.

Among these it is observed that in all the countries mentioned above the gold standard method of investigation is laparoscopy, while laparoscopy is regarded as the gold standard for definitive diagnosis, it is not always the first-line approach due to its invasive nature. As a result, in many countries the diagnosis begins with clinical evaluation followed by imaging

techniques like ultrasound or MRI before considering laparoscopy. Among these methods, transvaginal ultrasound is one of the most commonly used initial diagnostic tools due to its accessibility, non-invasiveness, and ability to identify certain types of endometriotic cysts.

Current Methods of Treatment of endometriosis

	India	New Zealand	Russia	China	Malaysia	USA
GnRH agonist	+	+	+	+	+	+
Combined oral contraceptives	+	+	+	+	+	+
NSAIDs	+	+	+	+	+	+
Progestins - medroxyprogesterone, dienogest	+	+	+	+		+
Selective Progesterone Receptor Modulators (SPRMS)	+					
Selective Estrogen Receptor Modulators (SERMS)	+					
Androgens – Danazol, GnRH Agonists, GnRH Antagonists, Aromatase Inhibitors, Letrazole.	+		+	+		+
IUD	+	+		+	+	+
Statins	+					
TNF-α Blockers	+					
Pentoxifylline	+					
Anti-Angiogenesis Factors	+					
Amitriptyline		+				
Cannabis		+				

Table 3. This table represents the current methods of conservative treatment of endometriosis used in India, New Zealand, Russia, China, Malaysia and USA. Among these it is observed

that GnRH agonist, Combined oral contraceptives and NSAIDs are most commonly used in all of these countries. Although these are popular methods and used widely, each of them have their own drawbacks which was discussed above.

First line therapies	India	New Zealand	Russia	China	Malaysia	USA
COCs	+	+	+	+	+	+
Progestins		+		+		+
NSAIDs	+			+	+	

Table 4. This table represents the first line of therapy used in India, New Zealand, Russia, China, Malaysia and the USA. It is observed that COCs are more commonly used as first-line therapy in most countries.

Nanoparticle selection and accumulation

- Selection Criteria for Nanoparticles

A number of variables need to be taken into account while choosing nanoparticles for endometriosis research:

-Biocompatibility [9]: Non-toxic and human-safe materials should be utilised.

-Targeting Ability: To improve targeted delivery, nanoparticles can be altered with ligands (such as peptides or antibodies) that bind selectively to receptors that are overexpressed on endometrial cells or lesions.

-Drug Loading Capacity: For treatment to be effective, nanoparticles must be able to encapsulate adequate amounts of therapeutic substances.

- Release Profile: Drugs are released into the body at the appropriate pace and place thanks to controlled release mechanisms.

Stability: To provide efficient transport without premature degradation, nanoparticles must maintain their stability in biological settings.

- Mechanisms of accumulation

Several processes contribute to the build-up of nanoparticles in endometrial tissue or lesions:

-Enhanced Permeability and Retention (EPR) Effect: Larger particles can accumulate more easily than smaller ones due to the leaky vasculature found in tumours. Drug distribution to endometriotic lesions can be improved by taking advantage of this phenomenon.

-Active Targeting: Researchers can promote targeted binding to endometrial cells or lesions and increase local accumulation by affixing targeting moieties to the surface of nanoparticles.

Phagocytosis by Immune Cells: Localised drug release may result from the absorption of some nanoparticles by macrophages or other immune cells that are present in the inflammatory milieu linked to endometriosis.

Selection of Animal Models

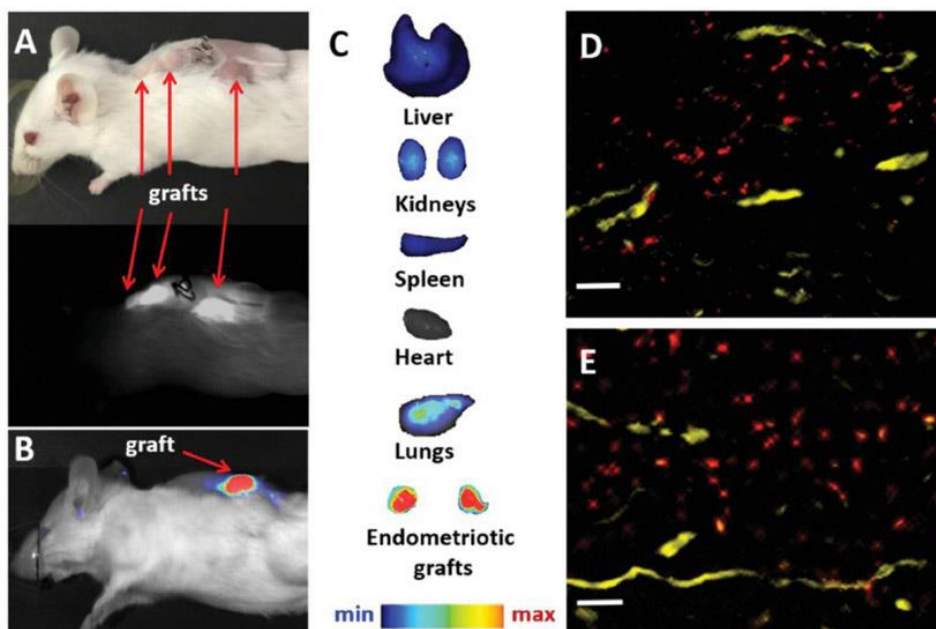


Figure 7- Animal model with the implanted graft and fluorescence imaging showing the graft
Biopsies of endometrium and endometriosis were collected from three adult rhesus macaques with advanced (Stage 4) endometriosis and transplanted subcutaneously into severe combined immunodeficient (SCID) female mice (four grafts per mouse). [3]

At the time of placement of graft, the animals were treated with implant releasing estradiol and progesterone to create artificial primate length hormonal cycle.

After two artificial cycles, the average graft “take” rate was $77.5 \pm 5.9\%$. Of the mice examined, 100% of the grafts displayed endometriotic glands and stroma and were immunocytochemically positive for oestrogen receptor 1 (ESR1) and progesterone receptor (PGR)

Presence of receptors demonstrates hormonal responsiveness of the grafts.

1. Animal Model: C57BL/6 mice**2. Reason for Selection:**

- Genetic Similarity to Humans: C57BL/6 mice are genetically similar to humans, making them a suitable model for studying human diseases, including endometriosis. Their genetic background allows researchers to draw parallels between the disease mechanisms in mice and those in humans.

- Established Endometriosis Models: C57BL/6 mice have been widely used in previous studies related to endometriosis, providing a well-established framework for researchers. This prior knowledge helps in comparing results across different studies.

- Immunological Relevance: This strain has a robust immune system, which is important for studying diseases that involve immune responses, such as endometriosis.

- Ease of Handling and Breeding: C57BL/6 mice are relatively easy to breed and maintain in laboratory settings, which is crucial for conducting experiments that require multiple generations or large sample sizes.

Loading the Animal with Nanoparticles**1. Nanoparticle Preparation:**

- The nanoparticles were specifically designed to encapsulate antisense oligonucleotides (ASOs). These ASOs target genes implicated in the pathophysiology of endometriosis, aiming to reduce the expression of these genes and alleviate symptoms associated with the disease.

2. Administration Method:

- The nanoparticles were administered through “intravenous injection”. This method was chosen because it allows for rapid distribution of the nanoparticles throughout the circulatory system, facilitating their delivery to various tissues, including those affected by endometriosis.

Nanoparticle based Imaging studies

Nanoparticle used	Magnetic iron oxide (Fe₃O₄)	SiNc-PEG-PCL
Type of imaging	MRI	Fluorescence imaging
Used as	Negative contrast agent	Contrast agent
Benefits	They require a simple injection or infusion of the material, followed	Reduced depth of penetration, but the fast acquisition, ease of use, and ability to be

	by non-invasive imaging of the tissues of interest.	incorporated into routine surgical procedures
Drawbacks	Requires effective delivery of the contrast agent to the targeted lesions. They may be retained in the body with unknown long-term consequences.	No drawbacks mentioned
Effect	Targeting of CD44 receptors that are overexpressed on endometriotic cells	Upon nanoparticle uptake by endometrial cells, the sinc molecules were released, activating their fluorescence
Results	Significant darkening of the walls of the lesions in mice that received HA-Fe ₃ O ₄ nanoparticles	24 h following intravenous injection, nanoparticles efficiently accumulate in, and demarcate, endometriotic grafts with fluorescence.

Table 5. Comparison between imaging studies of endometriosis using nanoparticles

** SiNc-PEG-PCL- silicon naphthalocyanine loaded poly (ethylene glycol)-poly(ε-caprolactone)*

KDR-MN therapy produced large patches of negative contrast linked to the lesions on MRI in a preliminary research including rhesus macaques with naturally occurring endometriosis. The specificity of the KDR-targeted nanoparticles for endometriotic tissues was validated by histological investigation, which verified the presence of endometriotic tissue at the locations determined by MRI. There was little evidence of off-target effects in non-target organs, suggesting the possibility of safe and efficient imaging and therapeutic approaches.

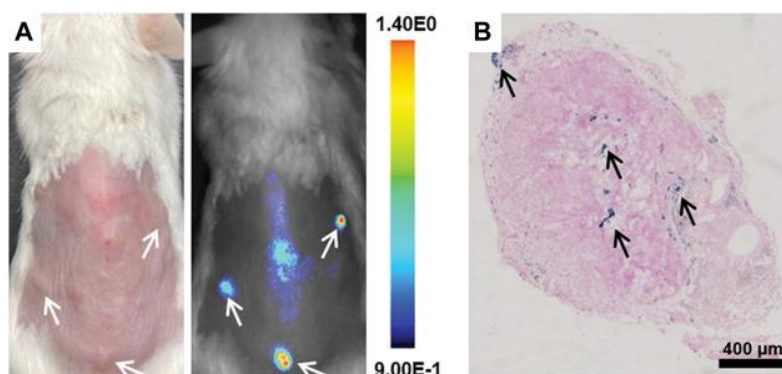


Figure 8- A) NIR fluorescence image of the mouse model of endometriosis treated with NIR fluorescence dye loaded KDR-MN. B) Prussian blue-stained sections of endometriosis grafts from the mouse model of endometriosis treated with KDR-MN.

In order to create a single-agent based nanoplatform that can perform near infrared (NIR) fluorescence imaging, SiNc was used as a building block. Activatable SiNc NP was administered into the tail vein of mice that each had four grafts. Activatable SiNc-NP gathers in endometriotic lesions, activates its NIR fluorescence 24 hours after a single injection, and accurately demarcates endometriotic lesions, according to whole-body photographic and fluorescence images of mice taken with the Fluobeam 800 and Pearl Impulse Small Animal Imaging System.

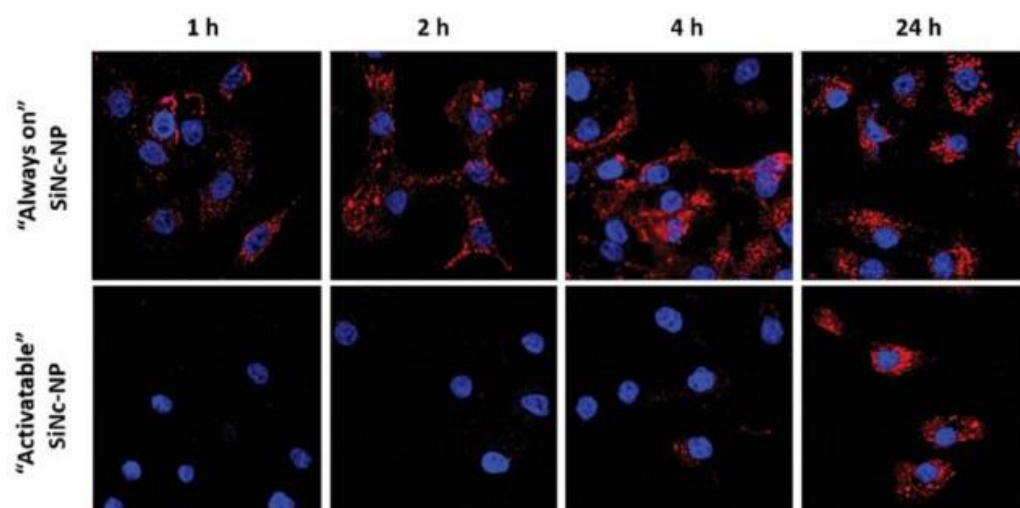


Figure 9 - Fluorescence microscopy images of macaque endometriotic stromal cells

Nanoparticle based Treatment modalities

Nanoparticle used	Nanoparticle-enhanced photothermal therapy (PTT) using flower-	SiNc-NP-Mediated Photothermal Therapy [2]	Magnetic Hyperthermia [8]

	like nano copper sulfide (CuS) and hollow gold nanoshells (HAuNS) coated with TNYL peptides [1] [4]		
Type of treatment	Laser Ablation	Laser Ablation	Thermoablation
Material used	NIR laser	NIR laser	Alternating magnetic field, hexagonal iron oxide nanoparticles doped with a small amount of cobalt
Benefits	Off target effects of PTT are extremely low, cells treated with heat are less prone to development of resistance	The employed light is safe for photo thermal therapy, because it is incapable of non-specific tissue heating during treatment	-
Drawbacks	Insufficient tissue penetration and the high levels of light intensity required to activate currently available photosensitizers	Limited tissue penetration of NIR light	-
Effect	Employs light-absorbing agents like NPs to convert optical energy into heat, selectively destroying targeted cells through protein denaturation and membrane damage	SiNc-NP rapidly increased the temperature inside of endometriotic grafts up to 47 °C upon exposure to NIR light	Uses an alternating magnetic field (AMF) to activate magnetic nanoparticles and thereby produce heat

Results	PTT is a viable, effective, and safe endometriosis treatment warranting additional study.	Treated grafts were completely eradicated within 4 days following a single treatment, with no recurrence in the 7-week study	The KDR-MN showed a higher retention rate in the grafts, leading to more effective heating. This treatment resulted in the elimination of endometriotic tissues in mice treated with KDR-MN.
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Table 6. Comparing different types of nanoparticles for the treatment of endometriosis.

Because of their adjustable optical characteristics, gold nanoparticles (AuNPs) have been extensively researched for photothermal therapy (PTT) in the treatment of cancer and have demonstrated enhanced therapeutic outcomes when paired with other imaging and treatment techniques [4]. Because AuNPs can experience localised surface plasmon resonance, which improves their interaction with light, they are the most often employed nanomaterial in PTT. Using hollow gold nanoshells (HAuNS) coated with TNYL peptides, which selectively bind to EphB4 receptors overexpressed in endometriotic lesions, Guo et al. created a targeted PTT system for endometriosis [1]. The significance of nanoparticle morphology on performance was further highlighted by a study that found that flower-like nano copper sulphide NPs had a 50% greater photothermal conversion efficiency than hexagonal sulphide NPs.

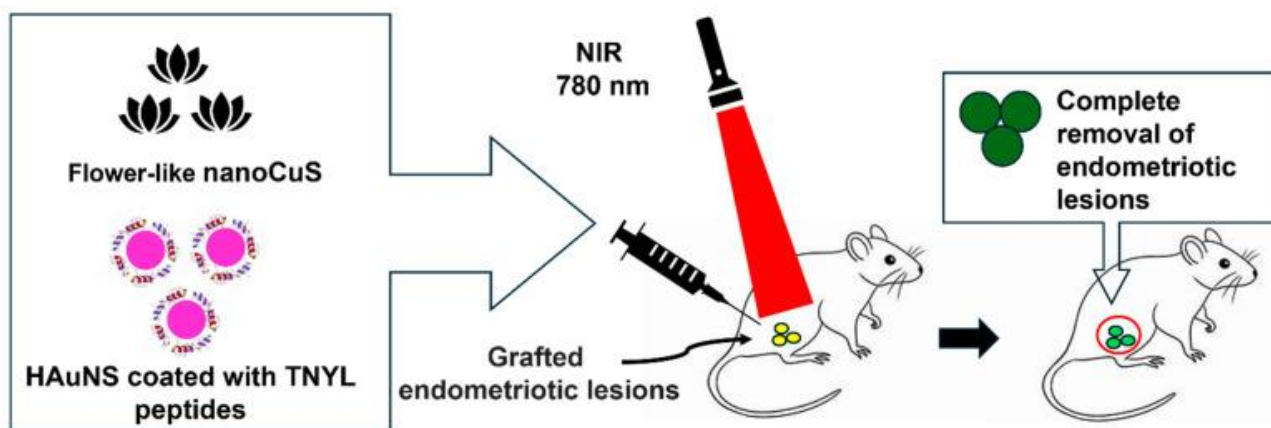


Figure 10 - overview of photothermal thermal therapy using flower like nanoCuS

In order to evaluate the efficacy of photothermal therapy for endometriotic lesions, "activatable" SiNc-NP was injected into the tail vein of mice that had received numerous grafts, four per mouse. For 15 minutes 24 hours after injection, two grafts in each mouse were exposed to NIR light (780 nm, 0.9 W cm⁻²), whereas the other two mice were used as

controls who did not receive NIR treatment. Temperature measurements revealed that after being exposed to NIR, SiNc-NP caused the treated grafts' temperature to rise to 47 °C. Within four days, the treated grafts were totally eradicated, and throughout the course of seven weeks, no recurrence was noticed

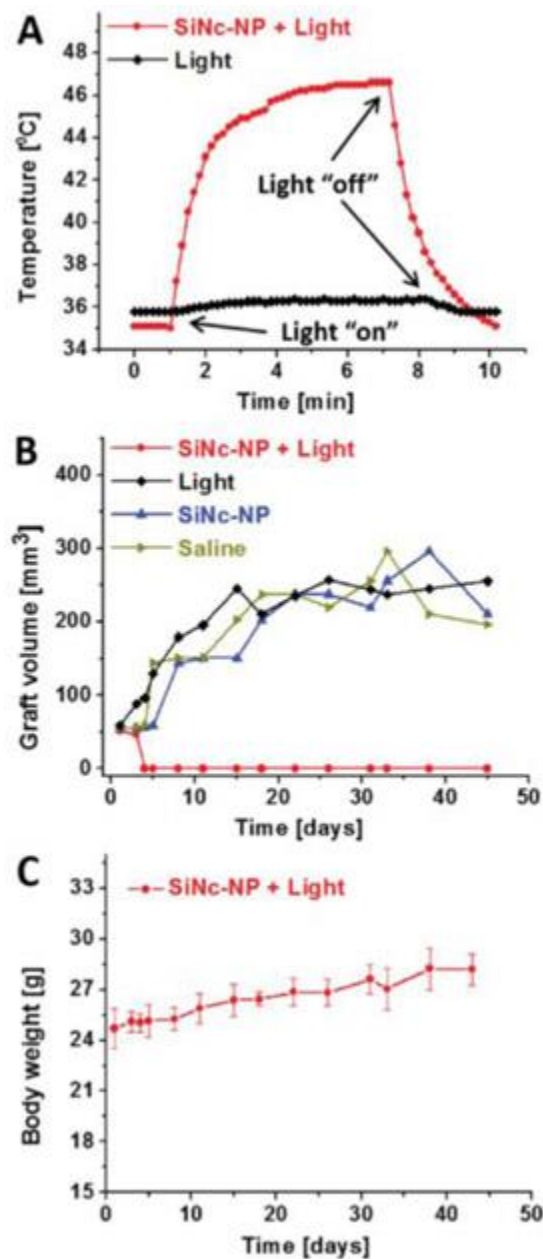


Figure 11- A) Temperature profile inside endometriotic graft upon exposure to 780nm of light, B) Growth profile of grafts after being treated with the mentioned materials C) Changes in body weight of the mice

The researchers assessed the ability of the KDR-MN to generate heat when exposed to an alternating magnetic field (AMF) after systemic injection. Five days' post-injection, the temperature in the grafts reached $51.6 \pm 1.2^{\circ}\text{C}$ with KDR-MN, compared to $49.3 \pm 1.8^{\circ}\text{C}$

with non-targeted nanoparticles. Both types of nanoparticles were able to raise the temperature above 46°C, indicating efficient passive targeting to endometriotic tissue. However, the KDR-MN showed a higher retention rate in the grafts, leading to more effective heating. This treatment resulted in the elimination of endometriotic tissues in mice treated with KDR-MN. Additionally, the nanoparticles were confirmed to accumulate in lesions in macaques with spontaneous endometriosis and could elevate the temperature in these lesions to 45°C when exposed to AMF.

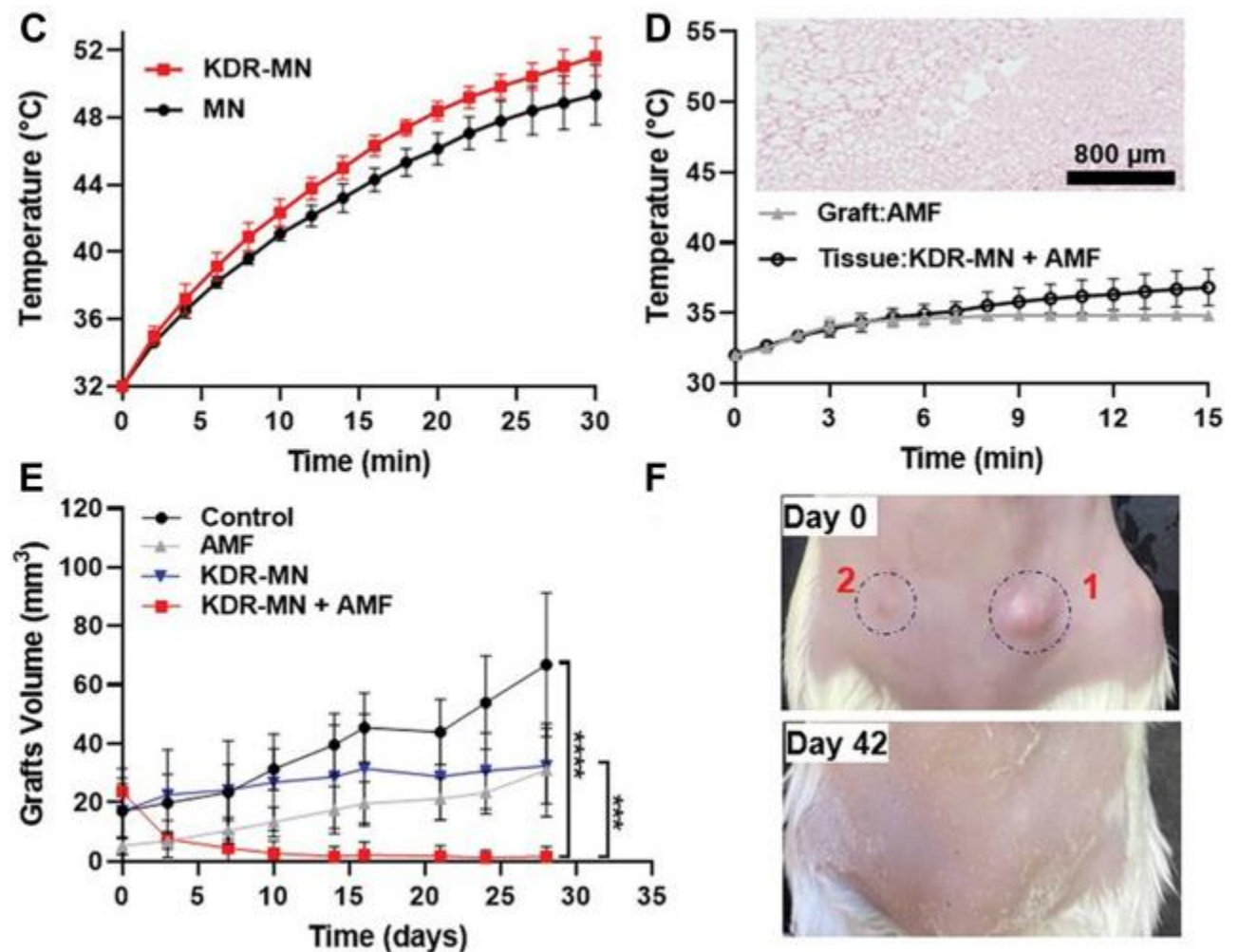


Figure 12 – C) temperature profile inside graft treated with NP, D) Temperature profile adjacent to the treated graft, E) F) Growth of the tissues over the days

Results

	NEUTRAL ARGON PLASMA	CO2 LASER [12]	HELIUM THERMAL	ELECTRODIATHERMY [13]	Flower-like nanoCuS and	SiNc-NP-Mediated PTT	MAGNETIC HYPERTHERMIA
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	[11]		COAGU LATOR [13]		HAuNS coated with TNYL peptides		
APPLIC ATION	Vaporizat ion, cutting, small vessel coagulati on	Tissue cutting and vaporization	Tissue cutting and vaporizat ion	Tissue cutting and vaporizat ion	Laser ablation using NIR laser	Laser ablation using NIR laser	Thermoab lation hexagonal Fe ₃ O ₄ NPs loaded in PEG-PCL carriers
SURGI CAL USE	No direct contact with the tissue	No direct contact with the tissue	No physical contact with the affected tissue	No physical contact with the affected tissue	Selective destruction of targeted cells through protein denaturatio n and membrane damage	Selective destructi on of targeted cells	Selective destructio n of targeted cells
VISUA L CUES	Light blue glow	-	-	-	-	-	-
INITIA L NUMB ER OF PATIE NTS / TYPE OF	20 (2 patients experien ced equipmen t failure)	50	192	192	Mouse (injection of rat uterine tissue)	Mouse (injection of monkey endomet riotic tissue)	Mouse (injection of macaque endometri um tissue)

PATIENT							
MEAN AGE	32 (20-49)	32(21-44)	29.03 (7.11)	28.99 (6.99)	-	-	-
MEAN GRAVIDITY	0.9(0-5)	-	-	-	-	-	-
MEAN PARITY	0.4(0-3)	-	-	-	-	-	-
STAGES OF THE DISEASE	5 patients had stage I endometriosis, 5 had Stage II, 4 had Stage III, and 4 had Stage IV	Deep Infiltrating endometriosis	Mild to moderate	Mild to moderate	-	-	Deep Infiltrating endometriosis
TOTAL LESIONS TREATED AND LOCATION OF THE LESIONS	46 lesions were safely vaporized with neutral argon plasma in locations including the	Adhesiolysis, ureterolysis, posterior fornix resection with laser, excision of DE infiltrating the	Ablation was performed on 36 women (40%) and excision was performed on	One (1%) ablation, 20 (21%) excision and 73 (78%) both	TNYL-HAuNS exhibited 2-fold higher accumulation in lesions than non-targeted HAuNS;	Treated grafts were completely eradicated within 4 days following a single	KDR-targeted magnetic nanoparticle (MN) accumulated in endometrial grafts, increased

	anterior cul-de-sac (15), ovaries (10), posterior cul-de-sac (7), pelvic sidewalls (7), pararectal spaces (2), fallopian tubes (2), broad ligament (1), uterine serosa (1), and rectal serosa (1)	uterosacral ligaments, full-thickness anterior rectal wall excision (selective excision of the bowel endometriotic lesion without opening of the bowel wall, recto sigmoid resection, and partial bladder resection.	seven women (8%); 47 women (52%) received both ablation and excision		PTT inhibited lesion volume by 92.7%	treatment, with no recurrence in the 7-week study	the temperature under an alternating magnetic field (AMF), and eliminated endometriotic lesions
POST OP REMARKS	All patients were discharged within 23 hours postoperatively. There	No IO or early complications were reported. All patients left the hospital, on average,	The patient was discharged home after approximately 4 hours.	The patient was discharged home after approximately 4 hours.	Inhibited the growth of the lesions, destroyed the structure of the lesions, decreased	PTT yielded >95% cell death in vitro and complete disease eradication	This study proposes that targeted magnetic hyperthermia is a potential non-

	were no intraoperative or postoperative complications. No further evidence of adhesions or disease when rebiopsied 7 weeks postoperatively.	within 3 days (range 2–9 days) after surgery. A significant improvement in pain was observed at the 3-, 6-, and 12-month follow-up in all patients. Thirty-five (70%) of the 50 patients were free of analgesic drugs on Day 2.			levels of TNF- α and estradiol	on without recurrence within 7 weeks in vivo	surgical and safe approach for eliminating deeply rooted endometriosis lesions.
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Table 7. This table represents a comparison between the laparoscopy and nanotechnology for the treatment of endometriosis.

*IO – intraoperative

Laparoscopy is an effective approach for diagnosing and treating endometriosis. Its minimally invasive nature offers significant advantages in terms of recovery time and postoperative discomfort while allowing surgeons to address both diagnostic and therapeutic needs in one procedure.

As for nanotechnology, it is increasingly recognized in the treatment of endometriosis due to its biocompatibility, targeted delivery, and low toxicity. Nanomaterials enhance drug delivery and treatment efficacy across various applications, including traditional therapies,

photothermal therapy, and magnetic hyperthermia. Table 7 summarises the effective use of nanomaterials for the treatment of endometriosis, it effectively eradicated the lesions and there was no recurrence recorded.

Conclusion

Given the lack of a cure and the challenges in diagnosing and assessing disease severity, innovative nanotechnology-based approaches are being explored to improve treatment and diagnostics for endometriosis. Nanoparticle technology represents a promising frontier in the research and treatment of endometriosis. By enhancing drug delivery systems through targeted accumulation at lesion sites, researchers aim to improve therapeutic outcomes while minimizing side effects. Continued investigation into nanoparticle design, targeting strategies, and clinical applications will be essential for realizing their full potential in managing this challenging condition.

In summary, both nanotechnology and laparoscopy present distinct advantages and drawbacks in the context of treating endometriosis. Nanotechnology offers innovative approaches with targeted therapies that may reduce systemic side effects but faces challenges related to clinical validation and regulatory approval. On the other hand, laparoscopy provides direct diagnostic capabilities and immediate treatment options but involves surgical risks and recovery considerations.

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