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Nanoparticles in the Treatment of Uterine Fibroids: Evidence from Animal and Human Cell Studies

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A B S T R A C T

Objective: Uterine fibroids are the most prevalent benign tumors among premenopausal women, often presenting with heavy menstrual bleeding, anemia, pelvic pain, and infertility. Conventional treatments, including surgical interventions and systemic pharmacotherapy, are frequently limited by adverse effects and incomplete efficacy. Recent studies have emphasized the potential of nanoparticles as targeted drug delivery systems, offering enhanced drug stability and bioavailability, reduced dosages, and improved therapeutic outcomes. This review aims to examine the primary types of nanoparticles utilized in the treatment of uterine fibroids.

Methods: A systematic search of PubMed, Scopus, Google Scholar, and Web of Science was conducted to identify studies published between 2010 and 2025 that investigated the use of nanoparticles in uterine fibroid therapy. Keywords included "uterine fibroid," "nanoparticles," "therapy," and related combinations. Both animal models and human cell studies were considered, with extracted data encompassing nanoparticle type, experimental model, dosage, therapeutic outcomes, and safety profiles, summarized in a comprehensive table. Review articles and preclinical studies lacking sufficient data were excluded.

Results: The analysis revealed that metallic and polymeric nanoparticles effectively reduced fibroid growth, suppressed Ki67 expression, and promoted apoptosis while enabling controlled drug release. Magnetic and peptide-based nanoparticles improved the efficiency of HSV-TK suicide gene delivery and selectively inhibited fibroid cell proliferation. Liposomal and electrospun nanoparticles enhanced cytotoxicity and reactive oxygen species (ROS) generation, modulating proliferation and epithelial-mesenchymal transition (EMT) pathways in a concentration- and drug-dependent manner.

Conclusion: Nanoparticles represent a promising, minimally invasive approach for uterine fibroid management. Various nanoparticle classes including metallic, polymeric, magnetic, peptide-based, and liposomal systems have demonstrated significant therapeutic effects in both animal models and human cell studies. However, clinical research remains limited, and long-term safety assessments are essential. Future studies should focus on pharmacokinetics, optimal dosing, and potential adverse effects in humans to facilitate the translation of these technologies into clinical practice.

Keywords: Uterine fibroids, Nanoparticles, Drug delivery systems, Gene therapy, Apoptosis, Targeted therapy

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Introduction

Women's health, particularly the prevention and early detection of gynecologic cancers, is critical for improving quality of life, preserving fertility, and reducing mortality, and remains a fundamental priority in public health [1-6]. Among gynecologic conditions, uterine fibroids represent a significant clinical concern. Uterine fibroids, or leiomyomas, are the most common benign tumors of the uterus in premenopausal women, with epidemiological data indicating that up to 70% of women experience some form of this condition during their lifetime [7]. These tumors originate from the smooth muscle cells of the myometrium and surrounding connective tissue and may present as solitary or multiple lesions of varying size [8]. While many fibroids remain asymptomatic and are often detected incidentally during pelvic examinations or imaging studies [8], some patients experience substantial symptoms, including abnormal or heavy menstrual bleeding, pelvic pain and pressure, urinary disturbances, constipation, anemia, and infertility, all of which can markedly impair quality of life [8].

The etiology of uterine fibroids is multifactorial, encompassing genetic, hormonal, and environmental influences [9]. Molecular studies have identified mutations, particularly in the MED12 gene, and epigenetic modifications in myometrial cells as key drivers of abnormal cellular proliferation and extracellular matrix accumulation [9]. Additionally, estrogen and progesterone receptors are overexpressed in fibroid cells compared to normal uterine tissue, and tumor growth is often hormone-dependent; postmenopausal reductions in hormone levels typically lead to fibroid regression [9].

Lifestyle and environmental factors further contribute to fibroid development and progression. Positive family history, early menarche, oral contraceptive use, obesity, vitamin D deficiency, diets high in red meat and low in fresh vegetables, and alcohol consumption have all been associated with increased fibroid risk [10]. These findings highlight the complex interplay of genetic, hormonal, and environmental factors influencing multiple cellular and molecular pathways [10].

The pathophysiology of uterine fibroids involves abnormal smooth muscle cell proliferation and excessive extracellular matrix production, which drive tumor growth and clinical manifestations [11]. Key signaling pathways, including PI3K/AKT/mTOR, MAPK, and Smad2/3, are modulated by hormones and growth factors, and their dysregulation promotes cellular proliferation, resistance to apoptosis, and localized angiogenesis [11,12]. Chronic inflammation and reactive oxygen species (ROS) generation further contribute to fibroid growth and stability [12].

Traditional treatment approaches include surgical interventions, such as hysterectomy and myomectomy, and systemic pharmacologic therapies, including GnRH agonists and progestins [13]. Although these strategies can reduce tumor size and alleviate symptoms, they are limited by rapid tumor recurrence, surgical complications, and drug-related adverse effects. Consequently, there is an increasing need for novel, minimally invasive approaches, prompting preclinical and clinical research into advanced therapeutic technologies [14].

In recent years, nanoparticles have emerged as a promising tool for targeted drug delivery [15]. These systems allow direct delivery of therapeutic agents to target tissue, enhance drug stability and bioavailability, reduce required dosages, and minimize systemic side effects [15]. Preclinical studies have investigated various nanoparticles, including metallic (silver, gold), polymeric (PEG-PLGA), magnetic, and peptide-based nanoparticles, which can exert therapeutic effects in animal and fibroid cell models via controlled drug release, inhibition of proliferative pathways, induction of apoptosis, and modulation of key signaling cascades [16].

Beyond drug delivery, magnetic and peptide-based nanoparticles can also transport therapeutic genes, such as HSV-TK, in a targeted manner, selectively reducing fibroid cell proliferation and inducing apoptosis [17]. Liposomal and electrospun nanoparticles have demonstrated the ability to enhance cytotoxicity, ROS production, and regulation of epithelial-mesenchymal transition (EMT) and proliferation pathways, with effects that are drug- and concentration-dependent, enabling personalized therapeutic strategies [18].

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Given these promising preclinical data, nanoparticles represent a novel, minimally invasive approach for uterine fibroid management [19]. However, clinical studies remain limited, and comprehensive evaluations of long-term safety, pharmacokinetics, and optimal dosing in humans are required. The development and translation of these technologies may improve treatment efficacy, reduce surgical interventions, and enhance the quality of life for patients with uterine fibroids.

Objective: This review aims to summarize the role of nanoparticles in inhibiting uterine fibroid growth and to provide a perspective on their potential clinical applications and the development of minimally invasive therapeutic strategies.

Methodology

This systematic review was conducted to evaluate the impact of nanoparticles on uterine fibroid growth, encompassing both animal and human cell studies. The primary focus was on nanoparticle type, dosage, route of administration, experimental model, therapeutic effects, and safety, providing a comprehensive overview of nanoparticle applications in fibroid treatment.

A comprehensive literature search was performed across major databases, including PubMed, Scopus, Web of Science, and Google Scholar. The search period spanned from January 2010 to December 2025, capturing the most recent preclinical and cellular studies relevant to nanoparticles in fibroid therapy.

The search strategy utilized a combination of relevant keywords, including “uterine fibroid” OR “leiomyoma,” “nanoparticles” OR “nanoformulation” OR “nanocarrier,” and “therapy” OR “treatment” OR “anti-fibrotic.” Boolean operators AND and OR were applied to combine terms, ensuring a comprehensive and focused set of results.

Inclusion criteria encompassed studies that:

Applied nanoparticles for fibroid treatment in animal models or human cell lines.

Provided complete information on nanoparticle type, dosage, experimental model, therapeutic outcomes, and safety.

Exclusion criteria included

Review or theoretical articles without experimental data.

Clinical studies unrelated to nanoparticles.

Studies focused solely on nanoparticle chemical characterization without assessing fibroid-related effects.

Data extracted from the included studies comprised

Nanoparticle type (e.g., silver nanoparticles, liposomes, polymeric nanoparticles).

Experimental model (human cells or animal models).

Dosage and route of administration (e.g., intraperitoneal, intravenous, or oral).

Treatment duration.

Therapeutic outcomes (e.g., inhibition of cell proliferation, induction of apoptosis, tumor volume reduction).

Safety and toxicity measures (e.g., LD50, side effects, tissue alterations).

This approach allowed a detailed comparison of nanoparticle types and their therapeutic efficacy, providing a solid foundation for future preclinical and clinical studies in uterine fibroid management. The search strategy, as well as the included and excluded studies, are illustrated in Figure 1.

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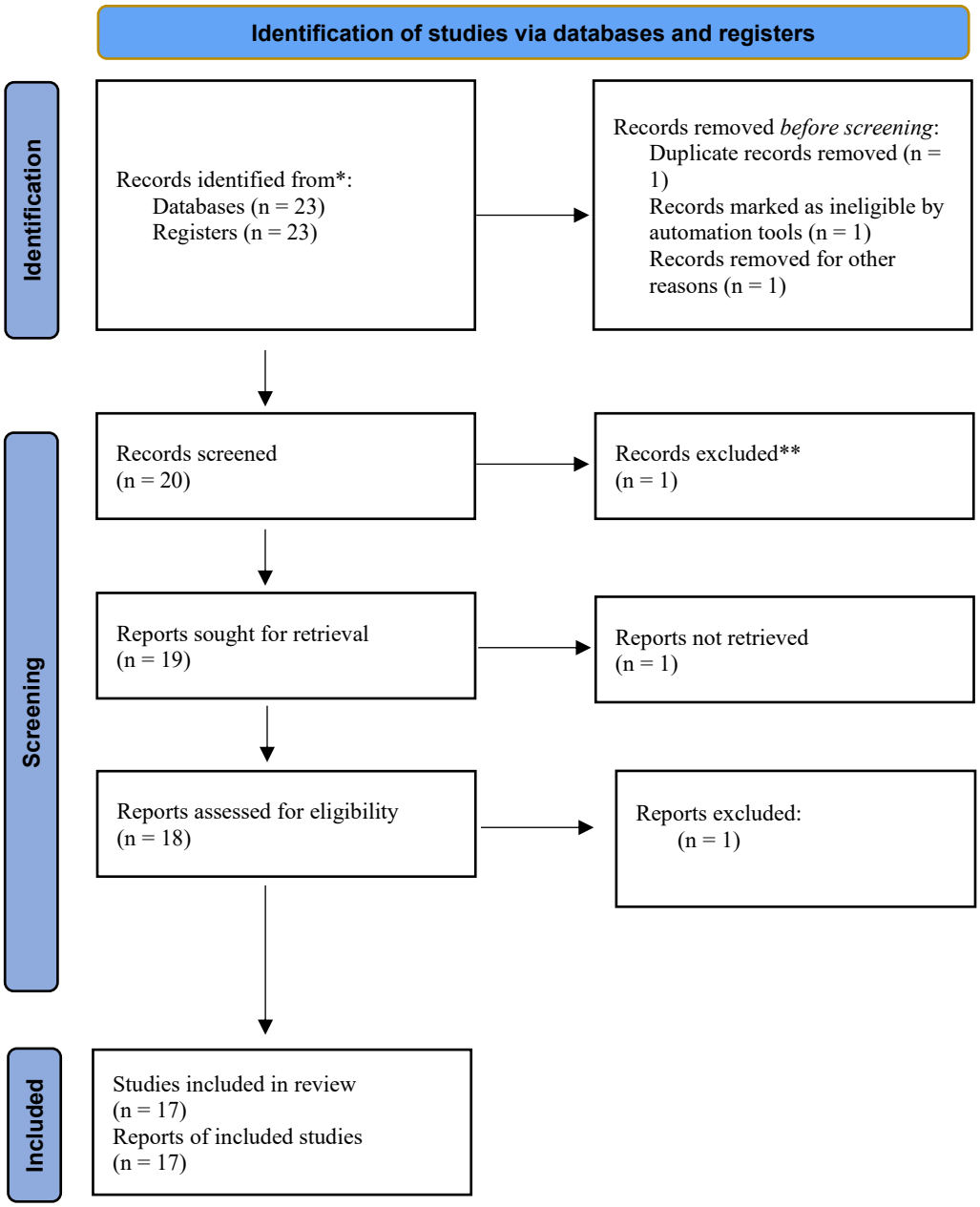


Figure 1. Flowchart of Search Strategy

Results

The reviewed studies indicate that a variety of nanoparticles including silver, magnetic, liposomal, and polymeric nanoparticles demonstrate significant potential in inhibiting uterine fibroid growth. Silver nanoparticles synthesized using *Polyscias fulva* were shown to reduce serum hormone and protein levels at therapeutic doses while preserving uterine structure; however, higher doses were associated with toxicity. PEG-PLGA and liposomal nanoparticles loaded with 2-methoxyestradiol and simvastatin effectively suppressed tumor growth, inhibited Ki67 expression, and induced apoptosis in fibroid cells.

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Liposomal and electrospun nanoparticles carrying anti-fibroid agents, such as ulipristal acetate and letrozole, enhanced cytotoxicity and reactive oxygen species (ROS) production, while modulating RON/PI3K signaling and epithelial-mesenchymal transition (EMT) pathways. Peptide- and DNA-based targeted delivery systems, functionalized with RGD ligands and anionic coatings, improved the delivery of the HSV1-TK suicide gene to fibroid cells, resulting in reduced cell proliferation and induction of apoptosis following ganciclovir treatment. Additionally, magnetic nanoparticles and electrochemical systems enhanced transfection efficiency and enabled precise targeting of fibroid therapeutics.

Collectively, these findings underscore the promise of nanotechnology as a minimally invasive, targeted, and effective approach for uterine fibroid management, providing a foundation for future clinical translation. Detailed results from preclinical and cellular studies are summarized in Table 1.

Table 1: Preclinical and Cellular Studies Investigating Nanoparticles in Uterine Fibroid Treatment

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Nanoparticle / Therapy	Target / Model	Dose / Experimental Conditions	Main Outcomes	Safety / Toxicity	Ref.
Green-synthesized silver nanoparticles from *Polyscias fulva* (PFAgNPs)	MSG-induced uterine fibroids in Wistar rats	50–2000 mg/kg BW	Reduced serum proteins, cholesterol, estrogen, and progesterone; preserved uterine structure	50–100 mg/kg safe; higher doses toxic/lethal	[19]
Magnetic nanoparticles (MNPs) with adenoviruses Ad-GFP and Ad-LacZ	Human fibroid cells and tumor-initiating stem cells	MOI: 1, 10, 50 + external magnetic field	Enhanced transfection efficiency, inhibited proliferation, induced apoptosis, improved suicide gene efficacy	Low viral dose safe	[20]
PEG-PLGA nanoparticles loaded with 2-methoxyestradiol (2-ME)	NOG immunodeficient mice with human fibroid xenografts	Intraperitoneal injection, 28 days; encapsulation efficiency 99.1%	51% inhibition of xenograft tumor growth ($P < 0.01$)	Data on efficacy; clinical safety requires further evaluation	[21]
Review	Overview of fibroid therapies and smart drug delivery using nanoparticles	–	Described the role of nanotechnology in enhancing bioavailability and efficacy	–	[22]
Liposomal nanoparticles loaded with simvastatin	NOG immunodeficient mice with bilateral human fibroid xenografts	Groups: control, simvastatin, simvastatin-NPs	Reduced tumor volume, Ki67 inhibition; effects similar to simvastatin, no significant difference	Low bioavailability and short half-life of simvastatin; NPs may enhance effect	[23]

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Phytochemical compounds (Dehydroxyelephantopin, Butein, Capsaicin, Fisetin, Kaempferol, Resveratrol, Silibinin, Curcumin)	Fibroid proliferation and inflammation models	–	Modulated Smad2/3, PI3K/AKT/mTOR, ERK1/2, and β-catenin pathways; reduced proliferation, inflammation, angiogenesis, and fibrosis	Non-surgical, personalized approach	[24]
PEGylated nanoparticles loaded with 2-ME	NOG immunodeficient mice with bilateral human fibroid xenografts	Intraperitoneal injection, 28 days; encapsulation efficiency 99.1%	51% tumor growth inhibition	–	[25]
Liposomal nanoparticles loaded with 2-ME	NOG immunodeficient mice with human PDX fibroids	50 mg/kg, IP three times/week for 28 days	30.5% tumor growth reduction, 55.8% Ki67 reduction, 67.5% apoptosis increase	Pharmacokinetics and safety require preclinical evaluation before clinical trials	[26]
Magnetic nanoparticles (MNPs) with αvβ3-targeted peptide DNA carrier (R6p-cRGD)	Targeted DNA delivery to fibroid cells	With ganciclovir treatment	Increased transfection efficiency; 20% suicide gene efficacy	–	[27]
Peptide nanoparticles with cysteine-polymer and histidine-arginine peptide, modified with iRGD	Targeted DNA delivery to fibroid and PANC-1 cells	–	Highest transfection efficiency; significant reduction of fibroid cells; suicide gene induction	–	[28]
Electrochemical dsDNA sensor on Au/GCE	Detection of fibroid drugs (mifepristone and cinnamic acid)	–	Sensitive, selective, stable detection; practical for drug screening	–	[29]
Arginine-histidine peptide carrier with cycloRGD ligand and anionic coating	Targeted DNA delivery to αvβ3-	–	Maintained polyplex stability; successful transfection in	–	[30]

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	positive fibroid cells (PLC)		serum; reduced PLC proliferation		
PEGylated AuNPs loaded with TNF-α (CYT-6091)	Enhancing conservative cryosurgery in ELT-3 model	5 μg TNF-α; pre-treatment 4 hours before cryosurgery	Reduced tumor growth; occasional complete eradication	Less toxic than native TNF-α	[31]
Liposomal nanoparticles loaded with ulipristal acetate (UPA-NS)	HEC-6 human fibroid cells	170.7 nm diameter, −18.2 mV surface charge, 90.57% encapsulation efficiency	70% cytotoxicity at 0.5 μg/mL; live cells reduced to 23%; increased ROS	–	[32]
Stable electrospun nanoparticles loaded with letrozole (LE/P188/PLLA)	Human fibroid cells	6.25–25% concentration; 145–173 nm particle size	Increased proliferation inhibition, induced apoptosis, modulated RON/PI3K and EMT pathways	Concentration-dependent	[33]
Liposomal nanoparticles loaded with 2-ME	NOG immunodeficient mice with human PDX fibroids	50 mg/kg, IP three times/week for 28 days	30.5% tumor growth reduction; 55.8% Ki67 reduction; 67.5% apoptosis increase (cleaved caspase-3)	Pharmacokinetics and safety need preclinical evaluation before clinical trials	[34]
Polycondensed peptide carriers with cyclic RGD ligand	Targeted DNA delivery to αvβ3-positive uterine fibroid cells	–	Threefold increase in transfection efficiency; successful HSV-TK suicide gene delivery; 2.3-fold proliferation reduction; apoptosis induction	Specific and effective suicide gene activity	[35]

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Discussion

Uterine fibroids are the most common benign tumors of the uterus in premenopausal women, often resulting in heavy menstrual bleeding, anemia, pelvic pain, and fertility issues. These complications significantly impair patients' quality of life, emphasizing the need for effective, minimally invasive therapeutic strategies [36].

Nanotechnology and nanoparticles have emerged as advanced tools in uterine fibroid management, enabling targeted drug delivery, enhanced bioavailability, and reduced systemic toxicity. Such approaches offer the potential to improve treatment efficacy while minimizing adverse effects [37].

Current evidence demonstrates that nanoparticles play a significant role in suppressing fibroid growth and may serve as effective, targeted, and minimally invasive therapeutic options. Silver nanoparticles synthesized with *Polyscias fulva* (PFAgNPs) were shown to reduce serum hormone and protein levels at therapeutic doses while preserving uterine structure; however, higher doses were associated with toxicity and mortality, highlighting the importance of defining a safe therapeutic window for clinical applications [19]. Polymeric PEG-PLGA nanoparticles and liposomal formulations loaded with 2-methoxyestradiol and simvastatin demonstrated enhanced tumor growth inhibition, reduced Ki67 expression, and increased apoptosis, reflecting improved bioavailability and controlled drug release [21, 23, 26].

Liposomal and electrospun nanoparticles carrying anti-fibroid agents such as ulipristal acetate and letrozole exerted direct cytotoxic effects, promoted ROS generation, and modulated RON/PI3K and EMT signaling pathways. These findings indicate that nanoparticles can effectively induce apoptosis and inhibit proliferation and fibrotic processes in fibroids, with their therapeutic efficacy influenced by physicochemical properties and targeted drug loading [32, 33].

Peptide-based targeted delivery systems functionalized with RGD ligands and anionic coatings enhanced DNA delivery to fibroid cells. The HSV1-TK suicide gene, combined with ganciclovir treatment, significantly reduced proliferation and induced apoptosis, providing a foundation for non-viral, minimally invasive gene therapy in uterine fibroids [30, 35].

Magnetic nanoparticles, in combination with peptide carriers and electrochemical systems, improved transfection efficiency and enabled precise drug detection within fibroid cells [20, 27, 29]. Collectively, these studies demonstrate that nanoparticles facilitate targeted drug delivery, controlled release, enhanced bioavailability, and reduced systemic toxicity, supporting the development of personalized and minimally invasive therapeutic strategies for uterine fibroids [22, 24, 25].

Integrating nanotechnology with conventional drugs, gene therapy, and recombinant agents may generate synergistic therapeutic effects, paving the way for future clinical studies and the development of minimally invasive fibroid treatments. Such approaches have the potential to reduce surgical interventions and improve patients' quality of life while minimizing adverse effects associated with traditional therapies [19–35].

Conclusion

Preclinical and cellular studies indicate that metallic, polymeric, magnetic, peptide-based, and liposomal nanoparticles possess substantial potential to inhibit uterine fibroid growth. By promoting apoptosis, suppressing proliferative pathways, and enabling controlled drug release, these targeted delivery systems improve therapeutic efficacy while reducing required dosages and limiting systemic side effects. Beyond drug delivery, magnetic and peptide-based nanoparticles enhance gene therapy by facilitating targeted gene delivery and selective induction of apoptosis. Nanotechnology also allows for the synergistic integration of pharmacological, gene-based, and conventional therapies, establishing a foundation for innovative uterine fibroid treatments. Despite these promising results, further clinical research is essential to evaluate long-term safety, pharmacokinetics, and optimal dosing in humans, which is critical for translating these technologies into routine clinical practice.

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