



Research Article

# Review on the USE of Nanotechnology in the Treatment of Uterine Fibroid Using Phytochemicals

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## Abstract

Uterine fibroids are the most prevalent gynecological disorder among reproductive-age women, with African American women experiencing the condition more frequently and with more severe symptoms than white women. Up to 70% of premenopausal women may develop fibroids by the age of 50, with symptoms that include abnormal uterine bleeding, prolonged and painful menstruation, pelvic pain, urinary problems, and, in some cases, infertility. The financial burden of managing uterine fibroids is substantial, and current pharmacological treatments are associated with hepatotoxicity and reduced bone density, while surgery remains the primary definitive treatment option. Given the growing interest in dietary phytochemicals and nanomedicine for the management of gynecological disease, this review examines the mechanisms of action of nanomedicine-based approaches with demonstrated efficacy against uterine fibroids. In various experimental models, natural compounds have demonstrated the ability to modulate key processes involved in fibroid initiation and growth, including cell proliferation, angiogenesis, fibrosis, and inflammation. Nanoparticles loaded with 2-methoxyestradiol and simvastatin have been shown to inhibit fibroid tumour growth in vivo in mouse models, suggesting considerable therapeutic promise. Nanoparticles have also been investigated for delivering magnetic hyperthermia to endometriotic tissue and show potential for hormone delivery, including transdermal hormone replacement therapy in postmenopausal women. This review summarizes current research findings on nanoparticle, and nanotherapeutic-based treatments for uterine fibroids.

## Keywords

Uterine Fibroids, Uterine Leiomyoma, Nanotechnology, Phytochemicals, Nanomedicine

## 1. Introduction

Uterine fibroids (UFs), or uterine leiomyomas, are the most common benign tumours of the female reproductive tract, affecting up to 70–80% of women by the age of 50. Although benign, fibroids represent a significant public health problem

because they cause abnormal uterine bleeding, pelvic pain, infertility, recurrent pregnancy loss, and impaired quality of life. The condition also imposes a substantial financial burden, with annual healthcare costs in the United States estimated at

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between US\$5.9 and US\$34.4 billion [4]. Epidemiologic studies further show pronounced racial disparities, with African American women experiencing a higher incidence, earlier onset, larger lesions, and more severe symptoms than women of other races [13, 16].

Uterine fibroids have a complex, multifactorial pathogenesis. Current evidence suggests that genetic susceptibility, steroid hormones, cytokines, growth factors, environmental exposures, epigenetic modifications, and alterations in the uterine microbiome all contribute to disease development [6, 14]. Nutritional factors have also been implicated: lower serum vitamin D and calcium levels have been associated with an increased risk of uterine fibroids in observational studies [9]. Fibroids are further characterized by excessive accumulation of extracellular matrix (ECM), which can make up a greater proportion of tumour mass than the smooth muscle cells themselves. Abnormal accumulation of collagen, fibronectin, proteoglycans, and other matrix proteins increases tissue stiffness, promoting tumour growth and progressive fibrosis [6].

Fibrosis in fibroids is driven by inflammation, tissue injury, angiogenesis, and impaired wound healing. Among the profibrotic cytokines involved, transforming growth factor-beta (TGF- $\beta$ ) plays a central role in extracellular matrix accumulation by stimulating collagen synthesis and inhibiting its breakdown [14]. Because of this, therapeutic strategies that combine anti-inflammatory, cytostatic, pro-apoptotic, and anti-angiogenic activity, together with inhibition of excessive ECM deposition, represent a rational approach to managing uterine fibroids. However, current treatment options remain limited. Hysterectomy is the only radical, curative procedure, but it is unsuitable for women who wish to preserve fertility. Conservative surgery, hormonal therapy, gonadotropin-releasing hormone agonists, and non-steroidal anti-inflammatory drugs offer only temporary relief and are often associated with significant side effects or disease recurrence after treatment is stopped. More recently, gonadotropin-releasing hormone antagonists such as relugolix have demonstrated efficacy in reducing fibroid-related symptoms and heavy menstrual bleeding, although their use may be limited by cost and other treatment-related considerations [1]. There is therefore a clear rationale for exploring treatment options that address the underlying pathophysiology of fibroids while improving patients' quality of life.

Phytochemicals derived from plants have attracted considerable research interest because of their broad range of biological activity, low toxicity, and ability to act on multiple disease pathways simultaneously. Many botanical compounds exhibit antioxidant, anti-inflammatory, anti-proliferative, and anti-fibrotic properties, making them attractive candidates for fibroid treatment [3, 7]. Despite promising preclinical data, however, the clinical application of most phytochemicals is limited by poor aqueous solubility, low oral bioavailability, rapid metabolism, and limited tissue distribution. These pharmacokinetic limitations have driven growing interest in nanotechnology-based drug delivery systems that can improve the

stability, bioavailability, targeted delivery, and therapeutic efficiency of phytochemicals [10].

Among the phytochemicals investigated for uterine fibroids, epigallocatechin gallate (EGCG), the principal catechin in green tea (*Camellia sinensis*), has generated the strongest pre-clinical and clinical evidence, making it an ideal candidate for nanoformulation-based therapeutic development.

## 2. Natural Products for the Management of Uterine Fibroids

Natural products have become a major focus of research for the treatment of uterine fibroids because of their multifaceted mechanisms of action across the molecular pathways implicated in disease development, including inflammation and oxidative stress [3]. Unlike conventional treatments, which typically act on a single pathway, these phytochemicals have multi-functional biological activity that gives them potential for long-term disease management.

Two of the most extensively studied natural products are epigallocatechin gallate (EGCG) and curcumin, although other phytochemicals, including *Scutellaria barbata* (barbed skullcap) resveratrol, and grape polyphenols, have also been investigated.

Despite their considerable therapeutic potential, these compounds are limited clinically by poor aqueous solubility, rapid metabolism, instability under physiological conditions, and low oral bioavailability. Recent research has therefore focused on nanotechnology-based delivery systems capable of improving their pharmacokinetic properties and therapeutic efficacy.

### 2.1. Epigallocatechin Gallate (EGCG)

EGCG is the principal catechin in green tea, accounting for nearly 80% of its total catechin content. Its antioxidant, anti-inflammatory, and pro-apoptotic properties have made it one of the most extensively investigated phytochemicals for uterine fibroid therapy [18].

Research has shown that green tea polyphenols inhibit several signalling pathways involved in tumour initiation and growth, mechanisms that have also been implicated in the development of uterine fibroids. EGCG has been shown to inhibit leiomyoma cell proliferation, reduce inflammatory signalling, and lower oxidative stress, while also promoting apoptosis in fibroid cells [12, 18].

Catechol-O-methyltransferase (COMT) is one of the principal molecular targets of EGCG. COMT is expressed at higher levels in uterine fibroids than in the adjacent myometrium and is thought to contribute to fibroid tissue growth. Zhang and colleagues demonstrated that EGCG inhibits COMT activity and reduces its gene expression in a dose-dependent manner, thereby reducing cellular proliferation and promoting apoptosis within fibroid tissue [18].

Experimental studies have consistently demonstrated substantial reductions in fibroid growth following EGCG treatment. In cultured leiomyoma cells, EGCG halted proliferation and induced apoptosis. In animal studies, oral administration of EGCG at 1.25 mg/kg/day produced approximately 80% shrinkage of uterine fibroid lesions, with no observed toxicity [17].

Clinical studies have similarly reported favourable safety profiles. In cardiovascular and metabolic research, daily doses ranging from 300 to 1000 mg have been administered safely over several months. Chow *et al.* [5] reported that 800 mg/day of EGCG was well tolerated, with mild, transient nausea observed only at the highest dose tested (1200 mg/day). Building on this safety and mechanistic evidence, conducted a pilot randomized controlled clinical study evaluating EGCG as a non-surgical treatment for symptomatic uterine fibroids [12].

## 2.2. Curcumin

Curcumin, the principal bioactive polyphenol in *Curcuma longa* (turmeric), has also demonstrated considerable therapeutic potential owing to its anti-inflammatory, antioxidant, anti-fibrotic, and anti-proliferative activity. Curcumin modulates several pathways implicated in tumour progression, including PI3K/Akt/mTOR, NF- $\kappa$ B, STAT3, and oxidative stress signalling [11].

Although direct evidence in uterine fibroids remains more limited than for EGCG, curcumin has been shown to inhibit abnormal cell proliferation, induce apoptosis, reduce fibrosis, and suppress extracellular matrix deposition across multiple disease models. Prior studies suggest that curcumin regulates leiomyoma growth partly through activation of peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ), leading to reduced proliferation and enhanced apoptosis.

Despite these promising biological effects, curcumin's poor water solubility, rapid metabolism, limited gastrointestinal absorption, and low systemic bioavailability substantially restrict its clinical usefulness. Nanotechnology-based delivery systems, including liposomes, polymeric nanoparticles, dendrimers, solid lipid nanoparticles, and micelles, have improved curcumin's stability, prolonged its circulation time, and enhanced its tissue penetration and therapeutic efficacy in preclinical cancer models [8, 11]. These advances suggest that similar nanoformulations may improve curcumin delivery to fibroid tissue and enhance therapeutic outcomes.

Curcumin has also shown synergistic effects when combined with other phytochemicals, including EGCG, piperine, resveratrol, and quercetin. These combinations enhance antioxidant activity, regulate autophagy, reduce mitochondrial dysfunction, and improve anticancer efficacy, particularly when delivered via nanoparticle systems [11].

## 2.3. Other Natural Products

Beyond EGCG and curcumin, several other plant-derived

compounds have shown anti-fibrotic activity. Grape-derived polyphenols, which contain catechins including EGCG, inhibit cellular proliferation and oxidative stress pathways associated with tumour development. Clinical studies have reported good tolerability of freeze-dried grape powder administered at doses equivalent to approximately 800 mg EGCG/day over several months, without significant adverse effects [5].

*Scutellaria barbata* has demonstrated anti-leiomyoma activity through inhibition of aromatase expression, suppression of insulin-like growth factor-1 (IGF-1), and induction of p27-mediated cell-cycle arrest [3]. Other phytochemicals, including resveratrol and quercetin, have also shown anti-inflammatory and antioxidant activity that may contribute to suppressing fibroid growth, although further clinical studies are needed to confirm their therapeutic efficacy.

## 3. Nanotechnology-Based Drug Delivery Systems

Nanotechnology-based drug delivery systems have emerged as promising strategies for improving the effectiveness of both natural compounds and conventional drugs used to treat uterine fibroids. Bioactive compounds such as EGCG and curcumin have demonstrated significant anti-fibroid potential; however, their clinical application is limited by poor water solubility, rapid metabolism, low bioavailability, and inadequate tissue distribution [11]. Nanocarriers help overcome these limitations by enhancing drug stability, prolonging circulation time, enabling controlled release, and improving drug accumulation at the target site [15]. Since the introduction of liposomes in the 1960s, nanotechnology has transformed drug delivery, leading to several FDA-approved nanomedicines with improved pharmacokinetic and therapeutic profiles [15]. Among the nanocarriers investigated — liposomes, polymeric nanoparticles, dendrimers, micelles, and gold nanoparticles each offers distinct advantages in drug loading, targeted delivery, tissue penetration, and controlled release, making them promising platforms for enhancing the therapeutic potential of anti-fibroid agents.

### 3.1. Liposomes

Liposomes are among the earliest and most widely studied nanocarriers for drug delivery, owing to their excellent biocompatibility and ability to encapsulate both water-soluble and fat soluble drugs [15]. They improve the stability, circulation time, and tissue-specific delivery of therapeutic agents. Preclinical studies have shown that liposomal formulations of compounds such as 2-methoxyestradiol and simvastatin can enhance treatment efficacy while reducing systemic toxicity in uterine fibroids [2]. Although liposomes also show promise for delivering natural compounds such as EGCG and curcumin, their clinical application remains limited by low drug-loading capacity, stability issues, and rapid clearance from the

body [11].

### 3.2. Polymeric Nanoparticles

Polymeric nanoparticles are among the most promising nanocarriers for uterine fibroid treatment because they improve the delivery of poorly soluble drugs by enhancing stability, bioavailability, and controlled release [2]. In a preclinical study, Ali *et al.* [2] developed biodegradable nanoparticles loaded with 2-methoxyestradiol (2-ME) that showed high drug encapsulation, sustained release, efficient uptake by uterine leiomyoma cells, and greater antiproliferative effects than the free drug, with PLGA nanoparticles demonstrating the best balance of efficacy and safety. More broadly, polymeric nanoparticles have also been recognized as effective carriers for natural compounds such as EGCG and curcumin, as they prolong circulation time, improve tissue penetration, and enhance therapeutic outcomes despite these compounds' inherently poor bioavailability [11, 15].

### 3.3. Dendrimers

Dendrimers are highly branched nanocarriers with numerous surface groups that allow efficient drug loading and modification with targeting molecules for precise delivery [11]. They have shown promise in improving the solubility, stability, and cellular uptake of curcumin, and can enhance targeted delivery to diseased cells through receptor-mediated uptake [15]. However, their application in uterine fibroid treatment remains limited, and concerns about the toxicity and immunogenicity of higher-generation dendrimers mean that further optimization and safety studies are needed before clinical use.

### 3.4. Micelles

Polymeric micelles are small, self-assembling nanocarriers that improve the delivery of poorly water-soluble compounds such as curcumin by increasing solubility, stability, and circulation time [11]. Their small size allows preferential accumulation in diseased tissue, while also enabling controlled drug release and the potential co-delivery of multiple therapeutic agents [15]. Although no micelle-based formulations have yet been reported specifically for uterine fibroids, their favourable delivery properties suggest they could be a promising platform for delivering EGCG and curcumin in future fibroid therapies.

### 3.5. Gold Nanoparticles

Gold nanoparticles are promising inorganic nanocarriers because of their unique optical properties, high drug-loading capacity, and easily functionalized surfaces, which enable targeted drug delivery, imaging, and theranostic applications [11, 15]. Although they have shown considerable potential in oncology research and have been identified as a platform for curcumin delivery, evidence supporting their use in uterine fi-

broid treatment remains limited. Further preclinical and clinical studies are needed to establish their safety, biodistribution, therapeutic efficacy, and clinical relevance in fibroid management.

### 3.6. Advantages of Nanocarrier Systems

Nanocarrier systems significantly enhance the therapeutic potential of natural compounds such as EGCG and curcumin by improving their stability, solubility, bioavailability, targeted delivery, cellular uptake, and controlled release, thereby overcoming major limitations of conventional formulations [11, 15]. These delivery platforms, including liposomes, polymeric nanoparticles, and micelles, also enable passive and active targeting, sustained drug release, and combination therapy, improving intracellular drug accumulation and antiproliferative effects against fibroid cells [2]. Additionally, nanotechnology supports the development of theranostic systems that integrate therapeutic and diagnostic functions, offering opportunities for more personalized, effective, and less toxic management of uterine fibroids.

## 4. Current Challenges and Future Perspectives

### 4.1. Current Challenges

Despite encouraging preclinical findings, several challenges continue to limit the clinical translation of nanotechnology-based therapies for uterine fibroids.

#### 4.1.1. Poor Clinical Translation

Most studies of nanoformulated EGCG, curcumin, and other phytochemicals remain confined to animal models. Relatively few clinical trials have evaluated these nanoformulations in humans, making it difficult to establish their long-term efficacy and safety, even where the parent compound (such as EGCG) has shown promising clinical outcomes on its own [11].

#### 4.1.2. Manufacturing and Scalability

Large-scale production of pharmaceutical-grade nanoparticles remains technically challenging. Reproducible synthesis requires strict control of particle size, surface charge, encapsulation efficiency, drug loading, and release kinetics, and batch-to-batch variability can significantly affect therapeutic performance and regulatory approval. Manufacturing must also comply with Good Manufacturing Practice (GMP) standards, increasing production costs [11].

#### 4.1.3. Regulatory Uncertainty

Regulatory pathways for phytochemical-loaded nanomedicines remain poorly defined. Regulatory agencies require

comprehensive characterization of nanoparticle composition, pharmacokinetics, biodistribution, biodegradability, toxicity, and long-term safety before approval, and many current nanoformulations lack sufficient toxicological and pharmacological data to satisfy these requirements [11].

#### 4.1.4. Safety Concerns

Although EGCG and curcumin are generally regarded as safe in their conventional forms, the long-term biological behaviour of their nanoparticle formulations requires further investigation. Nanoparticles may accumulate in organs such as the liver, spleen, kidneys, or lungs, potentially inducing oxidative stress, inflammatory responses, or immune activation, and their biodegradation products must be carefully evaluated to ensure long-term safety [11].

#### 4.1.5. Biological Barriers

Efficient delivery of nanoparticles to uterine fibroids remains challenging. Nanoparticles must evade rapid clearance by the reticuloendothelial system, avoid premature degradation, penetrate extracellular matrix barriers, and achieve sufficient accumulation within fibroid tissue, biological barriers that can substantially reduce therapeutic efficiency.

#### 4.1.6. Tumour Heterogeneity

Uterine fibroids exhibit marked heterogeneity in genetic mutations, vascularity, extracellular matrix composition, hormonal responsiveness, and growth patterns. A single nanoparticle formulation may therefore not be equally effective across all fibroid subtypes, underscoring the need for personalized therapeutic strategies.

### 4.2. Future Perspectives

Future research should focus on developing multifunctional, targeted, and stimuli-responsive nanocarriers capable of co-delivering EGCG, curcumin, and other therapeutic agents to improve treatment efficacy and minimize off-target effects. Hybrid and theranostic nanoparticle systems offer additional potential by enhancing drug loading, controlled release, targeted delivery, and real-time treatment monitoring for personalized therapy. However, well designed randomized clinical trials are essential to establish the safety, optimal dosing, pharmacokinetics, long-term efficacy, fertility outcomes, and comparative effectiveness of nanoformulated natural compounds in the management of uterine fibroids.

## 5. Conclusion

Nanotechnology-based drug delivery systems have the potential to overcome the major limitations of natural compounds such as EGCG and curcumin by improving their stability, bioavailability, targeted delivery, controlled release,

and therapeutic efficacy in uterine fibroid treatment. Although preclinical studies have demonstrated promising antifibrotic and antiproliferative effects, clinical translation remains limited by manufacturing complexity, regulatory uncertainty, long-term safety concerns, and the lack of large-scale clinical trials. Future research should prioritize multifunctional targeted nanocarriers, combination therapies, and well-designed clinical studies to establish safe and effective non-surgical treatments for uterine fibroids.

## Abbreviations

|                |                                                    |
|----------------|----------------------------------------------------|
| UFs            | Uterine Fibroids                                   |
| UL             | Uterine Leiomyoma                                  |
| ECM            | Extracellular Matrix                               |
| TGF- $\beta$   | Transforming Growth Factor-beta                    |
| EGCG           | Epigallocatechin Gallate                           |
| COMT           | Catechol-O-methyltransferase                       |
| PPAR $\gamma$  | Peroxisome Proliferator-activated Receptor Gamma   |
| PI3K           | Phosphoinositide 3-kinase                          |
| Akt            | Protein Kinase B                                   |
| mTOR           | Mechanistic Target of Rapamycin                    |
| NF- $\kappa$ B | Nuclear Factor Kappa B                             |
| STAT3          | Signal Transducer and Activator of Transcription 3 |
| IGF-1          | Insulin-like Growth Factor 1                       |
| 2-ME           | 2-Methoxyestradiol                                 |
| PLGA           | Poly(lactic-co-glycolic acid)                      |
| GMP            | Good Manufacturing Practice                        |

## Author Contributions

**Tenderwealth Clement Jackson:** Conceptualization, Project administration, Supervision, Writing – original draft, Writing – review & editing

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## Conflicts of Interest

The authors declare no conflicts of interest.

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