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Biomedical and Pharmaceutical Approaches for Uterine Fibroids: Current Methods and Recent Developments

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Abstract

Uterine fibroids are the most common benign tumours affecting the female reproductive route though a cheap and patient-friendly treatment is still yet to be developed. They cause heavy and irregular menstrual bleeding, anaemia, pelvic pressure and pain, abortion, and in some cases death, aside their socioeconomic and psychological impact. Currently the most widely practiced methods of treatments are either surgical removal of the fibroids (myomectomy) or the uterus (hysterectomy) which do not guarantee complete recovery or cause infertility. Medicine prescribed for this poorly understood disorder only suppress the symptoms rather than treating the patient, and they cause a plethora of side effects. Though some experimental biomedical approaches and phytotherapeutic agents may become more common in the future they require intensive research before they are widely used. Interestingly, smart drug delivery utilising nanotechnological approaches has not been widely studied for this disorder though it may be the treatment patients are looking for since they can enhance bioavailability, stability and allow active agents to be effective in low doses. This article reviews the nature of uterine fibroids, methods of treatment, their major drawbacks, a few novel applications that may be beneficial for patients in the future and finally compares the nanotechnological drug delivery systems and the interprets what these studies mean for the future of the patients suffering from this disorder.

INTRODUCTION

About 80% of women around the world suffer from the effects of uterine fibroids, which are solid, benign, gynaecological tumours with varying prevalence depending on age and race. These monoclonal, smooth muscle tumours, which can also be referred to as leiomyomas or myomas, can cause pelvic pressure, abdominal pain, abnormal uterine bleeding, anaemia, bowel and bladder irregularities, painful and/or irregular menses, impaired implantation, spontaneous abortion, infertility, and in some cases death. Though most uterine fibroids tend to be asymptomatic, the severity of the symptoms cannot be overlooked. Moreover, because they can remain asymptomatic for years when uterine fibroids exert symptoms their numbers and/or locations may be too risky for an operation [1–3].

The growth of these smooth muscle tissue is highly dependent on estrogen and progesterone. It is currently known that fibroids both react to estrogen within the bloodstream and synthesize estrogen through converting androgens by aromatase. It is also known that progesterone plays a crucial role in fibroid growth and expansion through its two receptor (PR) isoforms, PR-A, and PR-B. Though their role is not completely understood it has been observed that progesterone affects proliferation and extracellular matrix (ECM) structure thanks to recent animal studies and clinical trials. In fact, excessive production of ECM components such as fibronectin, laminins, and collagen happen to be characteristic properties of uterine fibroids. Numerous growth factors (Activin-A, fibroblast growth factors, Heparin-binding epidermal growth factor,

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etc.) are also considered to be contributors to uterine leiomyoma and myoma development, growth, and activities however, their sheer number and interdependency of metabolic pathways make them difficult to study precisely [4–6]. One of the facts known about fibroid formation is that it is initiated with somatic mutations. The most common chromosomal mutations encountered in patients are translocational mutations and trisomy on chromosome 12, deletion on chromosomes 3q and 7q, and rearrangements on chromosomes 6, 10, and 13. Recently a somatic mutation in the mediator complex subunit 12 (MED12) has attracted attention as it is tied to crucial etiological alterations encountered in fibroid structures, but not in the surrounding tissues and these mutations can be encountered in up to 85% of the patients. This highly conserved protein has a role in the transcriptional regulation of the RNA polymerase II complex. Any further insight on how this mutation is triggered and how crucial it is on the overall fibroid formation is still unreachable for the time being. Protein and transcriptional profiling of uterine fibroids have revealed that PI3K/AKT-mTOR signalling pathway is another common denominator discovered in patients suffering from uterine fibroids. It has been proven that this pathway is highly upregulated in patients and has been linked to the estrogen-dependent fibroid and myometrial growth. The exact order, cause, and triggers that lead to the formation of uterine fibroids may not be completely understood, but their effect on the surrounding tissue is well documented enough to form a theory. It is believed that inflammation of the myometrium triggers the synthesis of growth factors, hormones, and cytokines as a means of self-healing. What regularly should happen is that the released biochemicals trigger fibroblast formation which in turn to myofibroblasts. These structures release ECM components and are eliminated via apoptosis. If inflammation becomes chronic, however, myofibroblasts resist apoptosis which causes overexpression of ECM components and forces a transformation. Once a fibroid structure is formed, it can self-sustain. Moreover, the ECM can act both as a reservoir of growth factors and as

a physical stress factor that can trigger more fibroid formation[5,7,8]. Because uterine fibroid structures are so widespread, some patterns regarding the patient profile have been observed. Race of the patient seems to be one of the major factors, African descent patients are more likely to be affected by from uterine fibroids compared to women from other races. As the patient gets older, she is more likely to grow uterine fibroids, particularly if she had menarche at an early age. Though the actual mechanism is unclear, pregnancy seems to have a preventive effect. Obesity, smoking, high blood pressure, lack of exercise, alcohol and caffeine intake have been associated with a higher probability of uterine fibroid presence[9,10].

MEDICAL PROCEDURES

Surgical removal of the uterine fibroids (myomectomy) and uterus (hysterectomy) remains the most common treatment method and has been for decades. Though it is effective, it is also straining both the patient and the physician; hysterectomy is only suitable for patients who are comfortable with sacrificing their fertility whereas myomectomy can be affected by different variables such as the number, location, and the size of tumorous structures as well as the surgeon itself. Myomectomies may present a low rate of post-operation complications because it is uterus-sparing but they also come with the risk of re-occurrence of fibroidic structures and do not guarantee complete removal. It is for this reason that physicians should consult the most recent fibroid classifications developed by Federation of Gynaecology and Obstetrics (FIGO) in 2011. This classification describes eight different classes of fibroids according to their location and degree of intramural/intracavitary extension. Small subserosal and intramural fibroids tend to be asymptomatic and can go unnoticed for years [4,6]. When symptoms do arise, patients do not have much of a definitive treatment other than hysterectomy, alternative treatment methods come with their drawbacks. Hysterectomy is the only treatment that can be considered as completely successful but that is because this procedure removes the uterus tissue, resulting in the infertility of the patient. Myomectomy can be considered the second-best option and aims to preserve the child-bearing right of the patient by only removing the fibroid formations. However, removing the tissues does not address the main issue in the patient hence uterine fibroids can re-surface in the following years which can force the surgeons to perform a hysterectomy. Myomectomy can also cause hemorrhage, localized trauma, uterine rupture, and abnormal placentation while not improving

the chances for impregnation for certain. About a third of the removed fibroid structures can re-emerge and patients may prefer to go undergo a hysterectomy in the following years. Surgical operations performed on uterine fibroids cost billions of dollars annually with treatment and indirect costs [10–12].

As a medical intervention, uterine artery embolization is another option that physicians and patients may consider. In this minimally invasive procedure, tris-acryl gelatin microspheres or non-spherical polyvinyl alcohol is introduced to the patient through a catheter to the femoral artery. The introduced embolization agents, interrupt the blood supply to the whole uterus which triggers ischemic necrosis of the fibroids. The major drawback of this method is that it is not specific enough; since the embolization agents block the blood supply to the whole uterus, it has the risk of causing permanent damage to the tissue, going as far as causing infertility. Moreover, patients who go under embolization may suffer from fibroid reoccurrence[2,10,13]. In a recent randomized, multi-centre, open-label trial myomectomy was compared with uterine artery embolization in terms of quality of life. The trial prepared a questionnaire to the patients about their daily life and the changes they had experienced over 2 years. In this study, it was concluded that patients who went under myomectomy required fewer surgical reinterventions and had an overall larger quality of life assessment compared to the patients who went under uterine artery embolization[14].

Recently different technological approaches have been investigated to treat uterine fibroids. Magnetic resonance imaging-guided high-frequency ultrasound therapy (MRgFUS) is a non-invasive method of treatment approved by the FDA in 2004. This method, as the name suggests, relies on the imaging obtained through Magnetic Resonance Imaging (MRI) which is not only highly accurate but also can locate fibroids as small as 5 mm in diameter, even in abnormal locations. In this method, highly focused ultrasound waves are targeted to the locations where fibroids are detected in real-time which causes local coagulation necrosis. Not only it is highly precise and safe, but also patients can recover shortly after the procedure. However, it is time-consuming and cannot be performed on patients who suffer from multiple fibroids and/or fibroids with a diameter larger than 10 cm [15,16]. The most hindering aspect of this procedure is, that it relies on the patient lying down still within MRI equipment, which can cause other problems in long procedures. An alternative to MRgFUS that relies on the same treatment method is called transcervical fibroid ablation. In this method, a transducer is introduced through the cervix, and the position of fibroids is located with the help of a sonographic vision. The physician then places a needle electrode near if not on top of the fibroid where it delivers thermal energy enough to ablate the tissue. This technique is relatively new and its limitations are still unknown which is why it usually is not used on patients that have fibroid structures larger than 5 cm.s [17].

PHARMACOLOGICAL APPROACH

Shrinking uterine fibroids with the help of pharmacological agents is also possible, though cumbersome. Currently, the main goal of medical treatment for uterine fibroid is to dampen the immediate symptoms, which usually are, heavy menstrual bleeding, abdominal pain, and anaemia. To this end, patients are most likely to take combined oral contraceptives, progestogens, or nonsteroidal anti-inflammatory drugs (NSAIDs) to be able to handle the symptoms and live their daily lives. Though they are effective in modulating heavy bleeding and other side effects associated with the presence of fibroids; they do not treat the actual cause and can exhibit side effects in long-term use. Progestogens, for example, are the most commonly prescribed treatment for patients with uterine fibroids. They can reduce the amount of bleeding more than Levonorgestrel-Releasing Intrauterine System (LNG-IUS) which is a contraceptive designed to last for a long period (up to 5 years) and can reduce the amount of bleeding by almost 95% within the first year. However long-term use of progestogen can cause an increase in the amount of bleeding during or after the treatment and may trigger an increase in fibroid volume [6,18]. Gonadotropin-releasing hormone (GnRH) agonists or antagonists are some of the most effective and common methods of treating uterine fibroids. These pharmaceuticals compete with GnRH to bind to receptors resulting in the decrease of estrogen levels which in turn reduces the fibroid size. GnRH analogs are particularly useful when they

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are used as a pre-operative treatment since they can improve hemoglobin levels and reduce the amount of bleeding along with the fibroid size. If used for some time longer than half a year though, GnRH antagonists can cause a demineralization in bones, a decrease in estrogen levels, symptoms of menopause, disturbances in lipid and liver enzyme levels, and DNA damage on myoma cells [18–20]. NSAIDs such as ibuprofen or naproxen, have been used to treat abnormal uterine bleeding. They can do this by inhibiting cyclooxygenase enzyme which in turn limits the synthesis of prostaglandins. Though they can decrease menstrual cramps (dysmenorrhea) and blood loss, their effect on fibroids and the surrounding ECM is negligible. Tranexamic acid is an antifibrinolytic not only treats abnormal uterine bleeding better than NSAIDs but can also cause fibroid necrosis and infarction. It is a synthetic lysine derivative that can competitively block lysine-binding sites on plasminogen hence preventing fibrin degradation. Its effectiveness in reducing abnormal uterine bleeding allowed it to be approved by the FDA in 2009. Trials performed with this procoagulant drug revealed that though it is highly effective in treating the symptoms, tranexamic acid has no impact on ECM structure and the fibrosis it triggers can be painful for the patient and cause further infection [21–23]. Fibroid structures express higher levels of progesterone receptors, knowing this and using an inhibitor for this receptor allowed scientists to obtain a pharmaceutical molecule that binds to progesterone receptors. These selective progesterone receptor modulators (SPRMs) stop uterine bleeding, reduce fibroid size, inhibit cell proliferation, and decrease the ECM thickness within the endometrium. This group of chemicals has attracted a lot of attention recently, in particular, a molecule called Ulipristal acetate (UPA) which has a high bioavailability and can be used in long-term treatment. UPA is known to reduce heavy bleeding, improve anaemia and reduce fibroid volume. It has been studied for about a decade thoroughly, distributed to more than half a million patients as a pre-operative though some recent findings have caused scientists to be cautious. The first complication encountered with UPA is counter-intuitive; as the fibroid structure shrinks and the ECM gets thinner, surgeons have reported that removing structures from patients becomes harder to remove. Endometrial variations and liver toxicity were also linked to the uptake of UPA. Vilaprisan, Asoprisnil, and Telapristone are other formulations of SPRMs that are being studied, though their trials are still ongoing [24–26].

Recently, numerous scientists around the world have studied various natural compounds and their medicinal value to the point where plant-derived secondary metabolites have become a serious candidate for numerous disorders and diseases. Uterine fibroids are no exception to this concept; turmeric (*Curcuma longa*), green tea (*Camellia sinensis*), barbed skullcap (*Scutellaria barbata*), and winged spindle (*Euonymus alatus*) are only some of the herbal drug sources that have been used on uterine fibroids and have been observed to be effective thanks to their various and specific pathways[27,28]. Green tea may be one of the most widely studied plants not only for treating uterine fibroids but for health in general due to its prevalence. Even though *C.sinensis* is rich in terms of polyphenols, Epigallocatechin gallate (EGCG) is the most widely studied and the most promising polyphenol, particularly when it comes to uterine fibroids. It has been linked to antiproliferative, anti-angiogenic, antifibrotic, and pro-apoptotic activity as well as dysmenorrhea regulation. Turmeric was shown to exhibit antioxidant properties which allowed it to inhibit reactive oxygen species (ROS) dependent ECM proliferation processes and signalling pathways. This ability of the plant is tied to its main polyphenol, curcumin. This active molecule was used effectively against uterine fibroids in a few other studies where it was able to shrink fibroid structures, induce apoptosis and inhibit ECM proliferation. Resveratrol, berberine, lycopene, and sulforaphane are some of the other plant-based active molecules investigated as potential treatments for uterine fibroids *in vitro* . Some of these molecules have been used together with Vitamin D to observe if there would be a synergistic effect and indeed there was. Vitamin D was observed to improve the volume reduction capabilities of UPA and EGCG. Some common pathways of uterine fibroid treatment from phytopharmaceuticals (herbal pharmaceutic active molecules) are apoptosis induction, proliferation and/or ECM production inhibition, and anti-inflammatory effect. Though other pathways for uterine fibroid treatment may be observed the aforementioned effects seem to be the most common traits that plant-derived active molecules express on the tissue[29,30].

Table 1: The list of modern methods of treating uterine fibroids

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	Name	*Advantages*	*Disadvantages*	*Reference*
Biomedical Interventions	**Hysterectomy**	Only definitive mode of treatment Widely practiced since the '70s Efficiency is universal Improved quality of life post-operation Different routes are available	Definite infertility Costly High possibility of infection	[11,13,31]
	Myomectomy	Preserves fertility Alternative routes are available according to their size and/or location	Not definitive, follow-up surgeries may be required Damage to the surrounding tissue is a possibility Costly	[9,12,32]
	Uterine Artery Embolization	Minimally invasive hospitalization Rapid results	Fibroid structures may re-occur May cause infertility, miscarriage, infection, hematoma, thrombosis, or pseudo-aneurysm Patient satisfaction is not significantly larger than surgical intervention	[2,14,16]
	Magnetic Resonance Imaging Guided Focused Ultrasound (MRgFUS)	Short hospitalisation Low rate of morbidity Targets the fibroid, damage to the surrounding tissue is small	May cause irritation, skin burn, or localized numbness Not applicable to every patient Expensive and not widely available Fertility preservation is questionable Fibroid structures may re-occur	[1,13,28]

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	Name	*Advantages*	*Disadvantages*	*Reference*
	Intrauterine Sonography-Guided Radiofrequency Ablation	Fast acting efficient (up to 77% volume reduction within 6 months) Minimally invasive, incision-free Low rates of reintervention Applicable to fibroids with varying locations and sizes	Not common Its effects on fertility, possible infections, and endometrial cancer are still unknown	[10,33,34]
	Combined Oral Contraceptives	Widely available Easy to utilise	Has no effect on fibroid size or number Prescribed for alleviating symptoms, which has been under suspicion by researchers recently	[6,10]
Pharmacological Approaches	**Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)**	Widely available Low cost Few side effects	Not the most effective treatment Cannot be prescribed to patients with hypersensitivity	[10,19]
	Antifibrinolytics	Highly effective in reducing abnormal uterine bleeding Has been tied to the increased amount of necrosis in leiomyomas Its link to the possible increase in thrombosis has recently been absolved	Does not affect the fibroid structure May risk fertility	[31,35]

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	Name	*Advantages*	*Disadvantages*	*Reference*
	Selective Progesterone Receptor Modulators (SPRMs)	Thoroughly studied over the years by different study groups Can reduce the fibroid size along with fibroid-related symptoms Does not cause a loss in bone minerals and hypoestrogenic side effects Prevents further fibroid formation Tissue selective	Has been linked to liver damage to the point requiring transplantation May complicate further myomectomy procedures Can cause endometrial changes along with several side-effects Increased risk of fibroid re-occurrence	[2,6,36,37]
	Gonadotropin-releasing hormone (GnRH) agonists/antagonists	Have been studied thoroughly over decades of research Can reduce fibroid size along with abnormal bleeding and anemia, Improves pre-operative and postoperative hemoglobin levels as well as the quality of the surgery	Have been linked to a decrease in bone mineral density Can cause menopausal symptoms Discontinuation of the treatment allows the regrowth of fibroids Cannot be used longer than 6 months	[9,38,39]
Phytotherapeutics	**Curcumin from *Curcuma longa* (turmeric)**	Can affect fibroid-involved pathways Can induce apoptosis Inhibits proliferation, ECM accumulation	Obtained data are not always conclusive Has low bioavailability, solubility	[40–42]
	Berberine from *Scutellaria barbata* (barbed skullcap)	Reduces the hormone-dependent proliferative effect of fibroids Induces fibroid-specific apoptosis Has been linked to a reduction in fibroid size	There have not been many studies performed The results may not represent clinical conditions	[43,44]

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	Name	*Advantages*	*Disadvantages*	*Reference*
	Resveratrol (a natural polyphenol found in numerous plants)	Inhibits proliferation, induces apoptosis, and promotes cell cycle arrest Degrades ECM-related proteins	Increased concentration did not improve results Has low bioavailability and solubility Performed studies used doses higher than physiologically reasonable concentrations	[45–47]
	Epigallocatechin gallate from *Camellia sinensis* (green tea)	Has been linked to fibroid shrinkage, apoptosis induction as well as anti-angiogenic and antiproliferative activity Rapid results proportional to dose and duration Clinical trials regarding its safety and efficacy have been performed Symptoms arise with uterine fibroids have also been improved	Poor solubility, bioavailability, and stability Clinical trials with larger study groups are required for definitive results	[29,30,48]

FUTURE TREATMENTS

One common hurdle that herbal pharmaceuticals encounter preventing them from being widely practiced seems to be that they suffer from low bioavailability, instability, poor permeability, and possible toxicity depending on the dose. It is, for this reason, numerous studies have utilized nanotechnological approaches to use plant-derived active molecules effectively. By delivering active molecules directly at the site of interest with the lower dose, scientists can bypass the pharmacokinetic and pharmacodynamic challenges they would normally encounter which might push phytopharmaceuticals from *in vitro* to*in vivo* . Over the years numerous scientists around the world have successfully come up with different nanotechnological formulations to improve the pharmacological properties of phytotherapeutics as a way to find an herbal treatment [33,49–51]. Liposomes are spherical particles formed out of bilayer polar lipids which have a lipophilic and a hydrophilic end. As the liposome contacts water, the polar lipids self-assemble into a colloidal particle where the lipophilic ends are pushed towards the core and the hydrophilic ends arrange themselves towards the exterior, forming concentric bilayers that can encapsulate both hydrophilic and lipophilic molecules. These structures can deliver their load at a prolonged duration while increasing solubility and bioavailability resulting in improved intracellular uptake, biodistribution, and pharmacokinetics. So far, liposomes have been used to deliver quercetin, silymarin, ampelopsin, paclitaxel, actein, fisetin, curcumin, ginseng, berberine, palmatine, garlicin, rutin, wogonin, colchicine, breviscapin, catechins, and carotenoids successfully with

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improved characteristics. Most formulations tend to focus on cancer treatment, focusing on improving anticancer, anti-oxidant, chemotherapeutic, anti-inflammatory, and anti-angiogenesis activities. Liposomes' major drawback is their instability, especially when introduced intravenously. Active molecules obtained from botanical resources tend to be hydrophobic, making such structures almost ideal for delivering phytochemicals. The unique ability of phospholipids to self-assemble allowed scientists to synthesize a formulation where the active molecule is integrated within the carrier. This formulation technology has been patented by an Italian pharmaceutical nutraceutical company Indena under the name of Phytosomes® and has been proven to improve the absorption and bioavailability of herbal active molecules even when taken orally[34,52]. Nanoparticles are colloidal systems that range in size from 10 to 1000 nm. They can be composed of organic materials (polymers, proteins, lipids, and carbohydrates) or inorganic materials such as (gold, silver, iron oxide, silicon dioxide, etc.). Triptolide, flavonoids, lignans, taxel, berberine, tetrandrine, quercetin, polyphenols, turmeric oil, curcuminoids, ginger, silymarin, G*inkgo biloba* extract, resveratrol have been successfully integrated into various nanoparticle formulations for a menagerie of disorders by improving properties ranging from anticancer to brain function activation. The fact that nanoparticles can be obtained from a vast option of materials (which can be increased even further through structural modifications) combined with rich beneficial properties of phytotherapeutic molecules allows these formulations to be utilized in a wide range of applications. As advantageous as they are, nanoparticles can cause form aggregates which can make handling them challenging. Burst release and unpredictable toxicity due to size-related interactions are also other issues that can impede the practice of nanoparticles in medicine [53–55]. By altering the encapsulating agent to tailor the delivering agent to the disorder or disease it is possible to modify specificity and release rate. This procedure usually ends up increasing the diameter of the particulates from nanometres to micrometres. Rutin, camptothecin, quercetin, chelerythrine, and even various plant oils and extracts have been integrated into microspheres for their nutraceutical, hepatoprotective, anticancer, anti-inflammatory, antitumor, anti-oxidant, antiproliferative properties [34,56].

The fact that nanotechnological approaches improve bioavailability, pharmacological activity, and stability and reduce side effects such as toxicity by delivering smaller amounts of the active molecule directly at the site of interest is not a specific incentive for herbal formulations. The fact of the matter is many pharmacologically active molecules can benefit from these alterations, particularly chemotherapeutic agents, and hormone/hormone receptor-based formulations. Moreover, nanoparticulate delivery systems can protect the load it's carrying from physical and chemical stress preventing its degradation. One of the most characteristic alterations that fibroids exhibit compared to healthy cells is the structural and compositional changes on the ECM. It is known that uterine fibroids accumulate an excess amount of collagens (particularly Type-I and Type-II), fibronectin, laminins, and proteoglycans resulting in a stiffer environment. It is currently theorized that this stiffness is a cause of excessive bleeding and abdominal pain; meaning targeting the altered extracellular matrix may not only be logical for drug targeting but also reducing the stiffness can help with alleviating the symptoms[57–59]. Numerous studies have tried to utilize 2-methoxy estradiol (2-ME) for uterine fibroid treatments due to its apoptosis induction property and ability to inhibit DNA synthesis, proliferation, collagen synthesis, cyclin D_1, and B_1 expression, angiogenesis. 2-ME is also tied to microtubule disruption and interfering with several signalling pathways. Major drawbacks of this molecule are its low aqueous solubility, high plasma binding, and glucuronidation leading to poor bioavailability. Nanoparticles from poly (lactic acid) (PLA), and poly (lactic-co-glycolic acid) (PLGA) have been used to encapsulate this pharmaceutical molecule. It has been observed that the nanoparticle systems were indeed able to increase bioavailability and induce apoptosis. Similar to nanoparticles [59]. Borahay et.al. were recently able to add polyethylene glycol (PEG) to improve upon this study which reduced the phagocytic uptake and inhibit growth up to 51%*in vivo* at the end of a 28-day trial. In a different study, the same group utilized a liposomal formulation to deliver 2-ME to inhibit the growth of uterine fibroids. Inhibition growth of up to 30.5% was observed as early as 2 weeks [60]. A novel study utilized an adenovirus vector that encodes the herpes simplex thymidine kinase (*HSV-1TK*) suicide gene. This vector was then combined with magnetic nanoparticles, which allowed it to be transported to the desired locations by applying appropriate magnetic fields where the suicide gene can be deployed [61]. Magnetic nanoparticles were also observed to improve the effects of high-intensity focused ultrasound (HIFU) such as one used in MRgFUS. These nanoparticles not

only focus the energy to the desired locations, in turn reducing the damage exerted on the nearby healthy tissue, but they also can improve the heat conversion rate and overall performance[62].

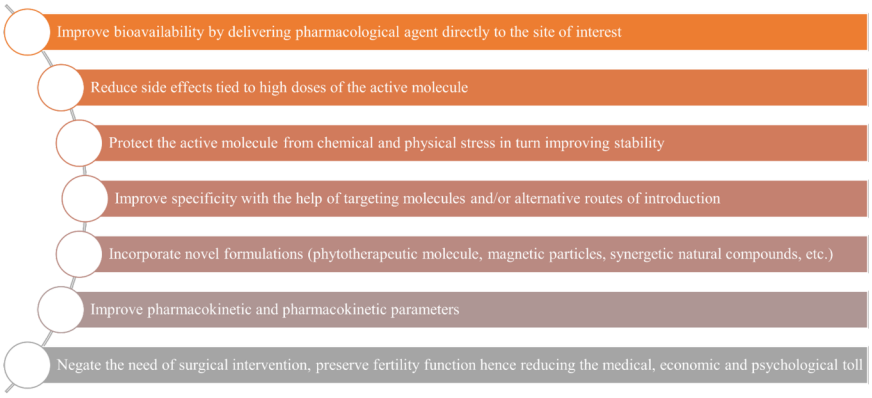

Figure 1: How nanotechnology can aid in uterine fibroid treatment

Table 2: Studies that have used smart drug delivery systems to treat uterine fibroids

Description
Poly(sebacic acid)-poly (ethylene glycol) complexes were used to encapsulate and deliver 2-methoxyestradiol *in vitro*
Nanoliposomes encapsulating 2-methoxyestradiol was shown to reduce fibroid size effectively *in vivo*
Magnetic nanoparticles complexed with adenovirus allowed the utilization of an external magnetic field for targeted gene th

DISCUSSION

Uterine fibroids affect the majority of women around the world, despite this fact little is known of these hormone-dependent monoclonal smooth muscle tumours. Their triggering effects are still unknown even though they can cause numerous physical, mental, and social setbacks. The most widely practiced method of treatment for this disorder is surgical intervention, either the fibroid structures are removed, or the entire uterus is, which results in the infertility of the patient. Currently, there are hormone and non-hormone-based treatments though each presents unique sets of drawbacks. Even myomectomy, the most extreme method of treatment following leiomyoectomy does not guarantee a complete cure since some structures may be too risky to remove or fibroids can re-grow. They are a burden on governments as they are on the patients; a cheaper, patient-friendly, and rapid treatment for this disorder is necessary. From the literature review performed, it can be said that nanoparticulate drug delivery systems have the most potential to reach an ideal treatment. However, because this technology is relatively new there are not as many scientific trials performed with them, let alone phase trials and patient surveys. Delivering a plant-based pharmaceutical molecule through a smart drug delivery system to uterine fibroids may result in better results considering they tend to be naturally biocompatible and biodegradable. Some phytopharmaceuticals have already exhibited great potential *in vitro* and proper translation of these results to *in vivo* will most likely be through nanotechnological drug delivery systems, considering these systems can by-pass many physical and chemical stress factors that traditional medicine has to endure and deliver their load directly at the site of interest at a desired rate. Its prevalence, severity, and challenges encountered in conventional treatment methods make uterine fibroids an ideal candidate to be investigated under the lens of nanotechnology. Moreover, the nature of uterine fibroids makes them quite favourable for targeted drug delivery systems. Uterine fibroids express a higher amount

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of progesterone receptors, meaning binding progesterone or competitively binding progesterone inhibitors to nanoparticulate drug carrier systems will be able to selectively deliver the pharmaceutical active molecule to the site of interest. Similarly, uterine fibroids express and accumulate higher amounts of ECM proteins such as collagen type-I and type-III or fibronectin. Targeting these molecules may also prove to be an effective path to induce specificity in carrier systems. Given that these targeting options are also present in healthy cells, albeit in smaller amounts, there comes the risk that the carriers may enter healthy cells. It is, for this reason, the carried load should not be toxic or poisonous on its own, rather it should trigger mechanisms that healthy cells can bring to a halt such as apoptosis or should take advantage of elevated pathways such as oxidation. Nanoparticulate systems may lose their stability or form aggregates which would decrease their efficiency. To get ahead of this, drug carrier systems should be introduced as closely as possible to the site of interest, the uterine artery, where the embolization agents are introduced might be a good candidate for this theoretical procedure.

Considering how widespread uterine fibroids are it is surprising to see how most modern methods of treatment accepted are not only patient-friendly but also occasionally cannot guarantee the non-reoccurrence of fibroid structures or the preservation of fertility. Different scientific studies around the world have investigated the nature of uterine fibroids from different angles resulting in a scattered yet comprehensive understanding of how uterine fibroids are formed (yet the exact reason, i.e. why uterine fibroids are formed remains to be a mystery) react to various pharmacological and medical treatments. By combining this scattered knowledge, it may be possible to come up with a patient-friendly, cheap, easy-to-obtain, and apply, consistent treatment for a disorder that threatens the majority of women around the world.

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Disclosure of Interest

The authors report that there are no competing interests to declare.

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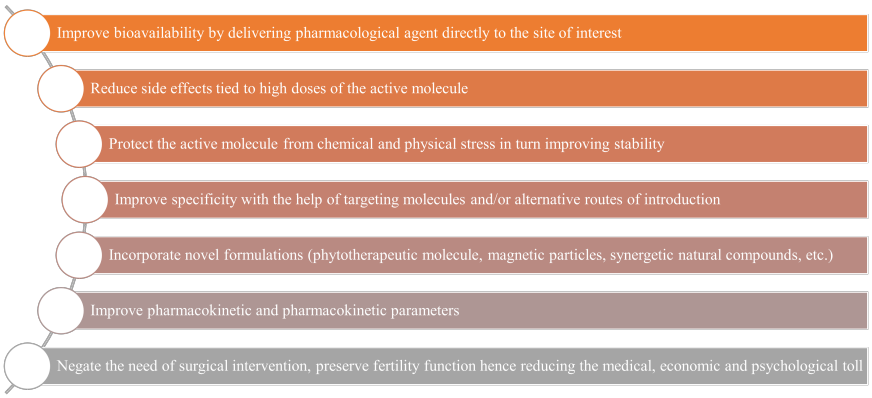

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