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Advancements and Emerging Therapies in the Medical Management of Uterine Fibroids: A Comprehensive Scoping Review

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Uterine fibroids, benign tumors originating from uterine smooth muscle cells, vary in prevalence depending on patient ethnicity, hormonal exposure, and genetics. Due to their high incidence, these neoplasms pose a significant burden on healthcare systems. Current treatment strategies range from routine monitoring in asymptomatic cases to surgical procedures such as myomectomy or hysterectomy in symptomatic patients, with an increasing trend toward uterus-preserving or non-surgical alternatives. This review examines the existing medical treatments for uterine fibroids and delves into the potential of emerging therapies.

A scoping review of the literature was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews.

Medical therapies are divided into hormonal and non-hormonal treatments; however, long-term, safe, and effective treatments in the treatment of uterine fibroids are limited. In addition to established therapies, there is an increasing number of studies investigating the effect of substances such as vitamin D or green tea extract on uterine fibroids. Some studies investigate acupuncture as a possible alternative therapy.

While existing treatments offer symptomatic relief and preparation for surgery, our findings point to a significant need for further research into long-term solutions, especially owing to recent limitations in the use of ulipristal acetate due to risk of liver damage. Initial studies involving vitamin D and epigallocatechin gallate are encouraging; however, additional research is required to establish definitive therapeutic roles.

Keywords: Anti-Inflammatory Agents • Non-Steroidal • Drug Therapy • Gonadotropin-Releasing Hormone • Leiomyoma • Tranexamic Acid • Ulipristal Acetate

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Introduction

Leiomyomas, commonly known as uterine fibroids, are benign tumors originating from the smooth muscle tissue of the uterus. These tumors are primarily composed of an abundant extracellular matrix that contains collagen, fibronectin, and proteoglycans. Each uterine fibroid is surrounded by a pseudocapsule, comprising tightly packed collagen, smooth muscle fibers, blood vessels, and neurofibers. The prevalence of uterine fibroids increases with age, reaching a peak during the fourth and fifth decades. Factors such as ethnicity, genetic background, and hormonal exposure significantly impact their development. Given their estrogen-dependent nature, fibroids are uncommon before menarche and generally shrink following menopause. Estimating the exact prevalence of uterine fibroids is challenging. A substantial number of them are asymptomatic and go unnoticed. Research indicates that uterine fibroid prevalence ranges between 5.4% and 77% in different populations, with approximately 30% of patients experiencing symptoms. Risk factors for uterine fibroids include age, reduced parity, early onset of menstruation, obesity, diabetes, polycystic ovary syndrome, and African descent [1]. Women with uterine fibroid-related symptoms often experience a reduced quality of life, impacting their emotional, physical, and social wellbeing [2].

Treatment options for uterine fibroids vary, ranging from routine monitoring in asymptomatic cases to surgical procedures, such as myomectomy or hysterectomy, in symptomatic patients. While hysterectomy is considered the definitive treatment for uterine fibroids, there is an increasing trend toward uterus-preserving or non-surgical alternatives, particularly among women who wish to avoid surgery or retain fertility [3]. Uterine artery embolization is the most widely recognized minimally invasive procedure. Ultrasound- or magnetic resonance-guided high-intensity focused ultrasound, although still experimental, show encouraging outcomes. Medical therapies are categorized into hormonal and non-hormonal treatments [1,4]. In addition to established therapies, there is an increasing number of studies investigating the effect of substances such as vitamin D and green tea extract on uterine fibroids [5]. Treatment choices are tailored to the patient's age, symptoms, reproductive goals, and other health conditions. Pharmacotherapy, while often suitable only for short-term use, remains a critical option for patients who are unsuitable for or opposed to invasive procedures [1]. To mitigate symptoms without resorting to hormonal or surgical interventions, some patients explore complementary and alternative medicine practices, such as physical exercise, herbal remedies, dietary changes, acupuncture, and physical therapy. However, the effectiveness of these methods is difficult to assess [6,7].

In this scoping review, we aim to address key research questions that are essential to understand current state and future directions of medical treatment for uterine fibroids: What are the current, effective treatment options available for uterine fibroids, and how do they compare in terms of efficacy and patient outcomes? What are the emerging therapies in the treatment of uterine fibroids and what is their potential in terms of efficacy and safety? Our objectives are to review and synthesize current medical treatments for uterine fibroids and to explore emerging therapies, including the investigation of new drugs and alternative medical approaches.

Material and Methods

A scoping review of the literature was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension for Scoping Reviews. The Cochrane and Pubmed databases were searched using combinations of keywords: "uterine fibroids" and "drug therapy", "tranexamic acid", "anti-inflammatory agents, non-steroidal", "ulipristal acetate", "gonadotropin-releasing hormone", "intrauterine devices, medicated", "danazol", "gestrinone", "contraceptives, oral, combined", aromatase inhibitors", "acupuncture", "vitamin D", and "epigallocatechin gallate". English language records published between 2010 and December 2023 in peer-review journals were included, to ensure an accurate interpretation and the analysis of current, high quality research. The exclusion criteria included articles written in languages other than English, individual case reports or case series, publications not focusing on gynecological diseases, and articles lacking an abstract. The evaluation process, conducted independently by 2 reviewers, was divided into 2 phases: an initial review of titles and abstracts, followed by detailed examination of the full text papers. To confirm the final selection of evidence, any discrepancies were resolved by consensus or by a third party. Information, including study design, sample size, treatment interventions, and outcomes, was extracted from the selected articles. Information regarding the approval of drugs for use was sourced from the websites of the Center for Drug Evaluation and Research (USA) and the European Medicines Agency (EMA) [8] (**Figure 1**). The findings were complemented by scanning the references of relevant reviews. Due to the diverse range of study designs, methodologies, and results of the articles included in this review, a calibrated form for data charting was not used. This scoping review, while systematic and structured, did not involve a formal review protocol. The methodology was adapted iteratively in response to the literature's evolving scope. The evidence was then synthesized, discussed within the context of the existing literature on medical treatments for uterine fibroids, and presented in tabular form (**Tables 1, 2**).

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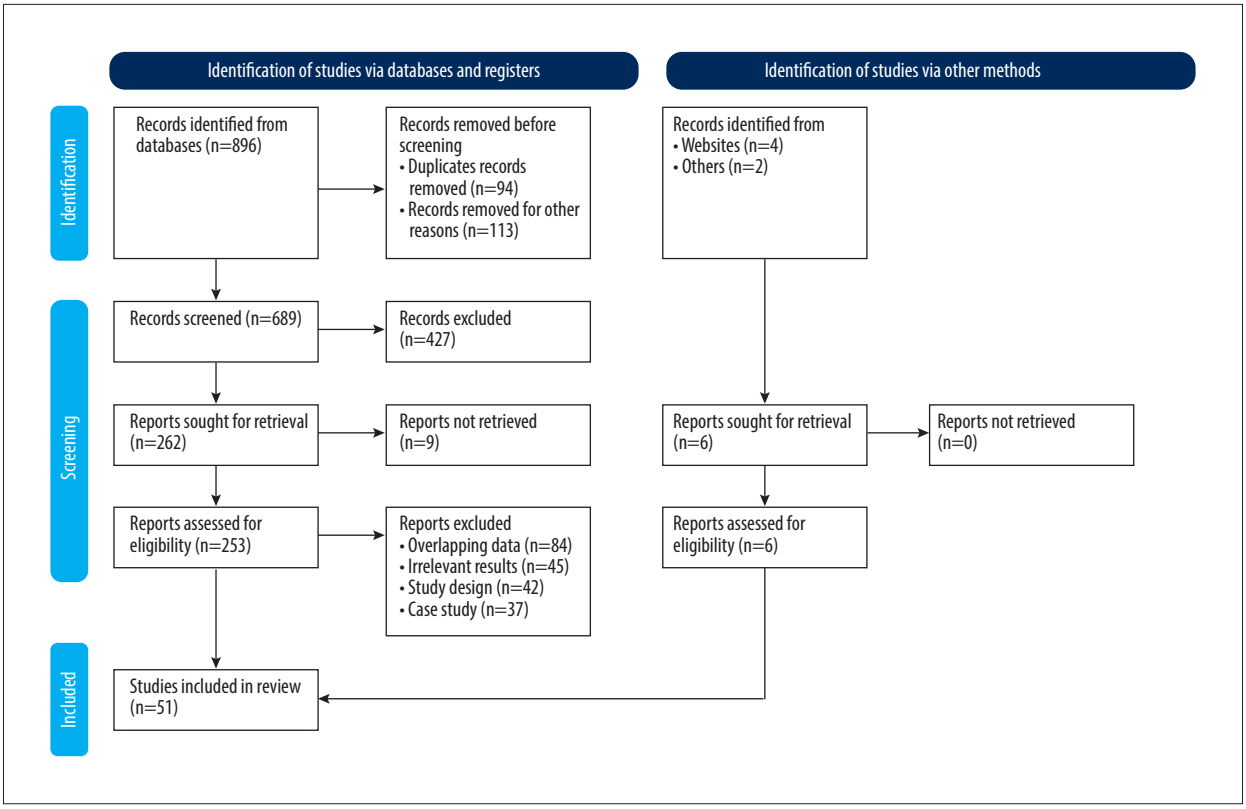

Figure 1. PRISMA 2020 flow diagram [8].

Results

Hormonal Treatment Options

GnRH Antagonists

GnRH antagonists, including elagolix, relugolix, and linzagolix, cause reversible suppression of the secretion of gonadotropins and ovarian hormones. They are effective in treating moderate to severe pain associated with endometriosis and abnormal uterine bleeding caused by uterine fibroids. GnRH antagonists are well tolerated and can be cost-effective; however, further research is required to compare their efficacy with that of oral contraceptives and progestins [9]. The duration of the therapy should not exceed 2 years. The most common adverse effects of GnRH antagonists are hot flushes, headaches, and bone loss. These adverse effects can be mitigated by hormonal add-back therapy (ABT). The most common ABT regimen is 1 mg estradiol and 0.5 mg norethindrone acetate [10]. Elagolix is approved by the U.S. Food and Drug Administration (FDA) for the treatment of uterine fibroids and endometriosis [11,12]. The EMA has approved relugolix for the treatment of fibroids, while approval for treating endometriosis is ongoing [13]. Linzagolix was under regulatory review in the United States until the withdrawal of its new drug application, and was recently approved by EMA for the treatment of uterine fibroids. The available form of linzagolix does not contain ABT. The dosage of linzagolix depends on the duration of therapy and whether ABT is used. It provides a treatment option for women with uterine fibroids who do not wish or cannot take ABT [14,15].

GnRH Agonists

Gonadotropin-releasing hormone agonists, such as triptorelin, leuprorelin, and goserelin, bind to the GnRH receptor, inhibiting the hypothalamic-pituitary axis and inhibiting female hormone secretion. They serve as a short-term treatment option for abnormal uterine bleeding and uterine enlargement associated with uterine fibroids. These agonists reduce fibroid size and decrease abnormal bleeding. However, their effect is temporary, with fibroids often returning to their original size within 3 to 9 months after treatment. Therefore, they are best used as a preoperative treatment option or as a bridging therapy to menopause or other medical therapies. In the preoperative context, they help increase hemoglobin and hematocrit levels before surgery and reduce intraoperative blood loss [15]. A comparative study of short-term administration of relugolix and leuproline in patients preoperatively showed similar benefits (uterine volume reduction and perioperative outcomes) and adverse effects [16]. Occasionally, they are used before uterine artery embolization [17]. The adverse effects

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Table 1. Current medical treatment options for uterine fibroids.

Treatment option	References	Current state of the art	Limitations	Future scope
GnRH antagonists	Donnez 2021; Giudice 2022; Elagolix FDA approval 2018, 2020; Linzagolix EMA approval 2022; ACOG 2021	Relugolix and linzagolix approved for the treatment of UF New Drug Application for linzagolix withdrawn in the USA	Limited duration of the therapy Hormonal add back therapy recommended to mitigate side effects	Safety evaluation of extended therapeutic regimens
GnRH agonists	ACOG 2021; Takeda 2022; Lee 2022	Effective in short term management of abnormal uterine bleeding and reduction in the size of UF	Limited duration of the therapy Hormonal add back therapy recommended to mitigate side effects UFs return to their original size in 3-9 months	Safety evaluation of extended therapeutic regimens
Levonorgestrel-releasing intrauterine device	ACOG 2021; Gerkowicz 2019; Kashani 2016	Effective, safe and reversible contraception Reduction in the quantity and duration of menstrual bleeding Endometrial hyperplasia prevention	Limited use in the cases of uterine cavity deformations or congenital uterine anomalies	Assessment of the viability of treatment time extension up to 8 years with single device
Depot medroxyprogesterone acetate	Harmon 2015; Harmon 2022	Long acting, injectable contraceptive Seems to decrease the risk of UF development	Data limited to studies on African American women	Comparative studies on other races
Combined oral contraceptives	ACOG 2021; Kwas 2021; Assiri 2022	Reduced menstrual bleeding Potential protective effect against UF	Contraindications to estrogen use such as breast cancer, liver disease, migraine with aura	Further studies to confirm protective effect against UF
Aromatase inhibitors	Committee opinion N. 663. 2016; Sayyah-Melli 2017; Mizoguchi 2016; Ando 2017	Reduction in size and symptoms of UF	Common side effects like hot flushes, bone loss, insomnia	Comparative research with other drugs Potential use of hormonal add block therapy
Gestrinone	Ciebiera 2017; Zhu 2012	Reduction in UF and uterus size	Very limited data, lack of randomized trials	Randomized trials to assess its safety and efficacy
Danazol	Kashani 2016	Reduction in UF size. Induction of endometrial atrophy	Very limited data Other drugs likely with superior effects	Comparative randomized trials to asses efficacy when compared with other treatments
Selective progesterone receptor modulators	ACOG 2021; Dinis-Oliveira 2021; Ulpristal Acetate use restriction 2021	Effective in the treatment of abnormal uterine bleeding Reduction in UF size	Limited indications after cases of severe liver damage possibly caused by ulipristal acetate	Further studies to assess safety and risk of liver damage
Selective estrogen receptor modulators	Chung 2014; Deng 2012	Reduction in UF size	No recent patient-based studies on safety and efficacy available	Randomized studies regarding its efficacy and patients' safety

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Table 1 continued. Current medical treatment options for uterine fibroids.

Treatment option	References	Current state of the art	Limitations	Future scope
Selective estrogen receptor degraders	Hernando 2021	Fulvestrant approved in the treatment of breast cancer	Uncertain impact on UF	Further research to assess their impact on UF
Tranexamic acid	14, 18, 35, 36 ACOG 2021; Kashani 2016; Fusca 2019; Eder 2013	Effective in reduction of menstrual blood loss	Gastrointestinal side effects Its effect may not be sufficient to prevent anemia	The use of tranexamic acid in combined therapy
Non-steroidal anti-inflammatory drugs	Bofill Rodriguez 2019	Reduction in menstrual blood loss	Limited evidence for its efficacy. Patients may still suffer from menorrhagia	Research regarding their use in combined therapy

UF – uterine fibroid.

Table 2. Emerging and alternative treatment options for uterine fibroids.

Treatment option	References	Current state of the art	Limitations	Future scope
Vitamin D	Ciavattini 2016; Krzyzanowski 2023; Markowska 2012	Inverse correlation between Vitamin D levels and UF Possible preventive effect	Limited data Data mainly on African-American women	Randomized trials on different races and in combined therapies
Green tea	Krzyzanowski 2023	Increased quality of life Possibly reduction in UF size	Limited data available	Studies to assess its impact on UF size
Clostridium histolyticum collagenase	Brunengraber 2014; Singh 2021	Reduction in UFs collagen density	Only one in vivo study identified	Further in vivo studies to assess efficacy and safety
Biodegradable thermoresponsive drug delivery systems	Taylor 2011	Novel drug delivery system	Very limited data on its use in UF	Further studies to assess its efficacy and safety with different drugs
Chinese herbal preparations	Lei 2023	Increased effectiveness of the combined therapy (Guizhi Fuling + mifepristone) vs mifepristone alone	Low quality of available data	High quality randomized trials to prove initial findings
Phytochemicals	Islam 2016; Lin 2019	Isoliquiritigenin causes diminished cell viability, proliferation, induces cell cycle arrest and apoptosis	Limited data	High quality randomized trials to prove initial findings
Curcumin	Malik 2023; Tsuiji 2011; Yilmaz 2018	Inhibition of tumor cell proliferation	Only in vitro and animal studies identified	Further animal and human based studies to assess safety and efficacy
Acupuncture	Zheng 2020 Zhang 2010	In Chinese medicine used to prevent and treat various diseases	Effect on UF is to be determined	Ongoing randomized trial

UF – uterine fibroid.

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of GnRH agonists include induced hypogonadism, menopausal symptoms, altered lipid profiles, and decreased bone density. Hence, using ABT is recommended to limit these adverse effects. Treatment duration typically lasts 6 or 12 months, based on which ABT is used [15].

Levonorgestrel-Releasing Intrauterine Device

The levonorgestrel-releasing intrauterine device (LNG-IUD) provides effective, safe, and reversible contraception. It works by inhibiting endometrial proliferation, thus reducing both the quantity and duration of menstrual bleeding and preventing endometrial hyperplasia in women receiving estrogen replacement treatment. In 2009, the FDA approved it for the treatment of heavy menstrual bleeding. As the LNG-IUD is effective for up to 5 years, it can be considered as long term treatment option for abnormal uterine bleeding. Although it does not alter fibroid size, it effectively reduces abnormal uterine bleeding associated with fibroids and can be used in symptomatic treatment. However, uterine cavity deformations due to fibroids or congenital anomalies increase the risk of IUD malposition, in some cases making this treatment unsuitable. Malposition rates are also higher in patients with a retroverted uterus and structural abnormalities, such as a septate or bicornuate uterus [15,18,19].

Medroxyprogesterone Acetate

Depot medroxyprogesterone acetate (DMPA) is a long-acting, injectable contraceptive. Artificial progestogens inhibit follicle maturation and suppress the synthesis of ovarian estradiol. Moreover, initial studies have suggested an inverse correlation between the use of DMPA and uterine fibroids [20]. In recent article based on the 5-year cohort of the Study of Environment, Lifestyle and Fibroids, Harmon et al explored the correlation between DMPA usage and the development of uterine fibroids. Among 1610 women aged 23 to 35 years, those exposed to DMPA in the last 2 years, compared to never users, exhibited a lower growth rate of uterine fibroids and a decreased risk of fibroid development (5.2% vs 10.7%). These changes in young women can potentially delay the onset of symptoms and minimize the necessity for invasive treatment [21]. Nonetheless, further studies are needed to support these findings.

Combined Oral Contraceptives

Combined oral contraceptives (COCs) are commonly used for symptomatic uterine fibroids, particularly in addressing heavy menstrual bleeding and dysmenorrhea. Although they do not reduce fibroid size, COCs significantly improve quality of life by alleviating associated symptoms and reducing blood loss in patients with heavy menstrual bleeding [15]. Some studies suggest a potential protective effect, particularly notable in the 30- to 40-year-old patient group, associated with long-term CoC use [22]. However, the use of COCs is not without its limitations. They increase the risk of venous thromboembolism and can be unsuitable for women with contraindications to estrogen use, such as a history of breast cancer, liver disease, or migraine with aura [23].

Aromatase Inhibitors

Aromatase inhibitors act by blocking aromatase, an enzyme essential for the production of estrogen. They are commonly used in the treatment of gynecological cancers [24] but have also been investigated as a potential treatment for uterine fibroids. Studies indicate that these inhibitors can reduce uterine fibroid size and symptoms in selected patients, although common adverse effects include hot flushes, mood swings, bone loss, and vaginal dryness [25]. In a randomized clinical trial comparing letrozole with combined therapy (letrozole and cabergoline) the size of fibroids was assessed. In both groups, reduction in uterine fibroid number and volume was observed, with no significantly important difference between the groups. Patients with combined therapy more often experienced headaches, with no significant difference in other adverse effects [25]. Notably, cases of successful use of aromatase inhibitors after hysterectomy in patients with intravenous leiomyomatosis and leiomyomatosis peritonealis disseminata have been described [26,27]. Further randomized trials are necessary for the widespread use of aromatase inhibitors in the treatment of uterine fibroids, including the use of ABT in treatment.

Gestrinone

Gestrinone, a synthetic steroid with anti-progestin and anti-estrogenic properties, has been studied for its effects on fibroid volume and overall uterine size, although data are limited. Its usage is associated with adverse effects such as acne, seborrhea, hirsutism, hot flushes, weight gain, breast size reduction, and headaches [28,29]. In meta-analysis of de Souza Pinto et al on endometriosis treatment, gestrinone showed a favorable safety profile; however, the evidence quality was low [30]. Data on the use of gestrinone in uterine fibroids are very limited, and no randomized controlled trials were found during this review.

Danazol

Danazol, a synthetic androgen with weak androgenic and antigonadotrophic effects, is associated with androgenic adverse effects, such as acne, hirsutism, and weight gain. As an antigonadotrophic drug, it induces hypoestrogenic symptoms, such as hot flashes, bone loss, and vaginal dryness. While danazol appears to reduce the size of fibroids while inducing endometrial atrophy and increasing hemoglobin levels, its exact mechanism of action in uterine fibroids is not clear. There is little

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research on the use of danazol in the treatment of symptomatic uterine fibroids, and it is likely that GnRH agonists show a superior effect in reducing fibroid size, compared with danazol. Further research is required if danazol is to be used more widely in the treatment of uterine fibroids [19].

Selective Progesterone Receptor Modulators

Selective progesterone receptor modulators (SPRMs), such as mifepristone, ulipristal acetate, vilaprisan, and asoprisnil, act as both progesterone receptor agonists and antagonists. Through their multi-mechanism action, they can provide effective control of menstrual bleeding and significant reduction of the volume of uterine fibroids. In 2008, asoprisnil failed third phase clinical trials, and ulipristal acetate was the first SPRM available on the market. Several clinical trials, including the PEARL I and PEARL II studies, have demonstrated the effectiveness of ulipristal acetate in reducing the size of fibroids, as well as in mitigating fibroid-related symptoms, while maintaining a favorable safety profile. Unfortunately, cases of severe liver damage possibly caused by ulipristal acetate use were reported, and indications for the use of ulipristal acetate in the treatment of uterine fibroids were severely limited [31]. Currently, this treatment is an option only for perimenopausal patients who are not eligible for surgery or when the surgical treatment has failed. Patients should be advised to monitor for signs and symptoms of hepatic injury. Regular monitoring of liver function is also recommended [15,32].

Selective Estrogen Receptor Modulators

Selective estrogen receptor modulators (SERMs) interact with estrogen receptors, exerting either agonist or antagonist effects, depending on the tissue type. Some studies suggested a correlation between SERM use and significant reduction in uterine fibroid volume. In an in vitro study involving human leiomyoma cells, decreased cell viability after SERM treatment was observed. However, the effect was more significant in the mifepristone and leuprolide acetate groups [33]. Despite these findings, data on SERM use in patients are limited and lack consistency. Thus, further studies are required to assess the viability of SERMs as a treatment option for uterine fibroids [34].

Selective Estrogen Receptor Degraders

Selective estrogen receptor degraders (SERDs) create a protein complex that causes the degradation of estrogen receptor protein. They have demonstrated efficacy in blocking tumor growth in breast cancer models, with fulvestrant being the first SERD approved for breast cancer treatment. While their impact on uterine fibroids remains uncertain, given the estrogen dependence of uterine fibroids, it may be beneficial to investigate the influence of SERDs on leiomyoma cells [35].

Non-Hormonal Treatment Options

Tranexamic Acid

Tranexamic acid, an antifibrinolytic drug, effectively prevents fibrin degradation. It is a non-hormonal treatment and has shown effectiveness in the treatment of menorrhagia and seems to be effective in fibroid-related abnormal uterine bleeding; however, data in this area are limited [15]. Tranexamic acid is beneficial before and during surgery. Its use during menstruation allows to reduce blood loss and increase the level of hemoglobin before the procedure. Intravenous administration of tranexamic acid immediately before or during surgery reduces perioperative blood loss, leading to a decreased risk of needing blood transfusion during or after surgery [36]. Notably, tranexamic acid does not increase the risk of venous thrombosis. Generally well-tolerated, its adverse effects are minimal, most often including gastrointestinal symptoms, such as nausea or vomiting. Other possible adverse effects include headache, back pain, and menstrual discomfort [19,37]. The role of tranexamic acid in treating fibroids requires further randomized trials. Nevertheless, its use in selected cases, especially in surgical preparation or during the perioperative period, is beneficial and is associated with reduced blood loss and lower complications risk.

Non-Steroidal Anti-Inflammatory Drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) have been shown to reduce menstrual blood loss. They act by inhibiting cyclooxygenase, thus reducing the synthesis or prostaglandins in the endometrium. A 2019 Cochrane review noted limited evidence for the efficacy of NSAIDs in the treatment of abnormal uterine bleeding, with mefenamic acid being the most researched drug. While NSAIDs reduce heavy bleeding, alternatives such as danazol, LNG-IUD, and tranexamic acid may be more effective. Although NSAIDs reduce heavy menstrual bleeding, some patients can still experience menorrhagia during treatment [38]. Still, NSAIDs are a viable supplementary treatment option for profuse vaginal bleeding associated with uterine fibroids, especially in patients not accepting or not eligible for other treatments.

Emerging and Alternative Therapies

Vitamin D

Vitamin D, a group of steroid compounds, plays a crucial role in cellular functions and calcium-phosphate balance. Vitamin D can be synthesized through sunlight exposure or obtained from the diet, predominantly from fatty fish, fortified foods, and supplements. Studies conducted so far have shown a reduced number of vitamin D receptors, as well as relative

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hypovitaminosis D, in the tissue of uterine fibroids than in normal myometrium [39-41]. Early clinical findings suggest an inverse correlation between vitamin D serum concentrations and the prevalence of uterine fibroids. In the future, vitamin D may become a component in both prevention and treatment of uterine fibroids; however, randomized trials are necessary to confirm preliminary results [5].

Green Tea

Epigallocatechin gallate (EGCG), the predominant catechin in green tea, is known for its antioxidant, anti-proliferative, and anti-angiogenic properties. It appears to promote apoptosis in uterine fibroid cells and decrease the levels of some proteins involved in cell-cycle progression. Several studies have analyzed the effect of EGCG on women. It seems to alleviate symptoms, increase quality of life, and, in some studies, was associated with reduction of uterine fibroid size. Further studies may pave the way for green tea EGCG-rich extracts as method of prevention and treatment of uterine fibroids [5].

Clostridium histolyticum Collagenase

Clostridium histolyticum collagenase (CHC) is made up of class I and class II collagenases, which possess binding capabilities with interstitial collagens. Approved by the FDA in 2010 for the treatment of Dupuytren contracture, CHC has garnered interest for its potential effect on uterine fibroids. In an ex vivo study conducted by Brunengraber et al, a decrease in uterine fibroid stiffness was noted following CHC injection [42]. Additionally, a study assessing the safety of CHC injection in women prepared for hysterectomy reported no significant adverse events, with injected fibroids demonstrating a 21% reduction in collagen density. Nevertheless, further research is needed to assess the viability of CHC as a treatment option for uterine fibroids [43].

Biodegradable Thermoresponsive Drug Delivery Systems

Biodegradable materials engineered for drug protection and delivery are currently under development, offering the potential for drug administration via a single injection. These drugs exert their effects locally, while the delivery system gradually degrades over a specified period of time. These advancements hold promise for women seeking to avoid more invasive procedures in the future [44].

Chinese Herbal Preparations

Chinese herbal preparations, particularly the Guizhi Fuling formula, have emerged as a promising treatment option of uterine fibroids. These preparations exert their effects through various mechanisms, including the modulation of hormone levels, induction of apoptosis, and inhibition of fibroid cell proliferation. A recent meta-analysis suggested the potential superiority of combined therapy involving mifepristone and Guizhi Fuling capsules, compared with mifepristone alone. However, authors emphasized the low quality of available data and underscored the need for high-quality randomized trials to prove initial findings [45].

Phytochemicals

Plant-derived compounds, known as phytochemicals, exhibit disease-preventive characteristics and contribute to the vibrant coloration of plants. These beneficial compounds are plentiful in a variety of foods, such as fruits, vegetables, grains, legumes, nuts, and seeds. Among the diverse array of phytochemicals are flavonoids, carotenoids, and polyphenols, renowned for their capacity to modulate cellular processes including proliferation, inflammation, fibrosis, apoptosis, and angiogenesis [46]. Isoliquiritigenin, a chalcone flavonoid employed in traditional Chinese medicine, has shown promise in inhibiting estrogen-induced fibroid growth in models of uterine leiomyoma and uterine smooth muscle cells. It diminishes cell viability and proliferation, induces cell cycle arrest, and fosters apoptosis through diverse molecular pathways [47]. With further investigation, isoliquiritigenin could emerge as a novel therapeutic avenue for uterine fibroids.

Curcumin

Curcumin, derived from turmeric (*Curcuma longa*), demonstrates potential in inhibiting the proliferation of various tumor cell lines. Despite its recognized efficacy, the precise mechanism through which it operates remains unknown. Recent investigations using mice models with a human leiomyoma xenograft have unveiled curcumin's inhibitory prowess. Notable reduction in xenograft growth alongside diminished matrix protein production was observed. Moreover, investigations conducted in vitro using Eker rat-derived uterine leiomyoma cell lines have highlighted the significant inhibitory effect of curcumin on cell proliferation [48,49]. In another rat model study, it was demonstrated that curcumin effectively mitigated oxidative stress and histological damage induced by cyclophosphamide treatment [50]. However, to firmly establish the therapeutic potential of curcumin in treating uterine fibroids, extensive research encompassing both animal and human studies is necessary to validate initial findings.

Acupuncture

Acupuncture, a longstanding practice in Chinese medicine used to prevent and treat various diseases, has yet to show definitive effects on uterine fibroids. A randomized controlled trial to determine the influence of acupuncture on symptoms related to uterine fibroids is ongoing. Further research is necessary to

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determine if acupuncture has the potential to become treatment option for uterine fibroids [6,7].

Discussion

Inherent to the design of this scoping review are certain limitations. Primarily, our inclusion criteria, restricted to English studies, may have led to the exclusion of relevant research published in other languages. Furthermore, while not using a calibrated form for data charting is in line with the nature of a scoping review, it may have limited the uniformity in data extraction and synthesis.

While we recognize the limitations and findings of our research, there are also several potential positive implications. First, our review emphasizes the need for further research into long-term, noninvasive treatment options for uterine fibroids, especially in the context of recent restrictions on the use of drugs, such as ulipristal acetate, which was the only drug with the potential for long-term treatment that allowed for reduction in the size of fibroids. It was useful in preoperative treatment of patients with large fibroids, suspected difficult surgery, and/or anemia caused by fibroids. Unfortunately, due to cases of severe liver damage, its preoperative use is no longer allowed. Currently, ulipristal acetate is recommended only for patients in which surgery failed or who are not eligible for operative treatment [15,31,32]. The safety and efficacy of GnRH antagonists combined with ABT were investigated for up to 2 years. Additionally, investigations involved drug withdrawal after 52 weeks of combined therapy. After therapy cessation, most patients experienced heavy menstrual bleeding relapse. In these patients, symptoms were effectively alleviated by retreatment [51]. However, further research on longer treatments, involving drug-free intervals between treatments, is necessary.

Furthermore, the promising initial results from studies on vitamin D and EGCG suggest new possibilities for future investigations and therapies [5,39-41]. Several compounds identified in this review, including vitamin D, EGCG, and curcumin, show potential in uterine fibroid prevention and symptom mitigation [5,48]. With further research, they could play a role in the prevention and treatment of uterine fibroids, potentially leading to a reduction in asymptomatic and symptomatic cases. Alternative therapies, such as Chinese herbal preparations, phytochemicals, and novel drug delivery systems, show promising initial results. However, the majority of studies identified in this scoping review were conducted in an in vitro or ex vivo setting [44-50]. Randomized studies involving large cohorts of patients are necessary to assess the safety, efficacy, and clinical utility of potential new therapies.

Finally, the insights gained from this review have the potential to inform clinical practice, offering a broader perspective on available and upcoming treatments.

Conclusions

Currently available medical treatment options for uterine fibroids offer primarily symptomatic treatment. Pharmacological treatments help reduce the symptoms and prepare patients with anemia for surgical treatment. In selected cases, it serves as a bridge therapy until surgical treatment or menopause, when most fibroids spontaneously decrease in size and the symptoms associated with them subside. Several drugs and dietary components are being studied for their role in uterine fibroid development and treatment; however, well-planned randomized trials are necessary to draw firm conclusions. While invasive treatment remains the only definitive solution, further studies on medical treatment of uterine fibroids are needed to establish long-term therapies.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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