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REVIEW

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A comprehensive review comparing conventional versus traditional remedies in the treatment of endometriosis with futuristic insights

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Abstract

Background A common condition known as endometriosis typically takes place in females in their reproductive age and develops generally in the endometrial lining of females. Chronically, endometriosis has been associated with a reduction in the patient's quality of life (QOL) which can have a hazardous impact on their social working and functionality. Owing to the involvement of hormones in the development of endometriosis, drugs having the capability to modulate the hormonal concentrations, along with surgical techniques, have been designed to treat endometriosis.

Main body There are certain drawbacks of the currently existing therapy for endometriosis which include the inability to improve the quality of life of the patient, treatment failures and unresponsiveness from the patient, and adverse effects of the drugs such as weight gain, mood swings, vaginal dryness, etc. Herbal medicines have attracted the attention of various researchers for the development of novel therapeutics against several gynecological disorders, mainly endometriosis. Our present review summarizes the precise pathogenesis of endometriosis along with its conventional therapy and novel developments in herbal medicines wherein we have compiled data from 15 completed clinical trials (conventional therapy: 7, herbal therapy: 8). Additionally, we have included data from four preclinical studies on herbal medicine that showed promising results in treating endometriosis highlighting the necessity for clinical trials to yield more definitive findings. The number of clinical trials carried out to assess the response of herbs in endometriosis is limited which is why additional studies could provide beneficial concrete evidence in the effective treatment of endometriosis and ensure improved patient outcomes.

Conclusion Conventional therapies possess certain limitations to treat endometriosis due to which the attention of scientists has shifted toward herbal therapy due to its advantages such as improved safety and tolerability in treating endometriosis. However, additional clinical investigations into herbal therapy may prove to be fruitful in the discovery of novel therapeutics to treat endometriosis effectively.

Keywords Estrogen, Progesterone, Conventional therapy, Herbal therapy, Endometriosis, GnRH agonist

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Background

The endometrium constitutes the deepest layer of the uterus located within the female reproductive system, and it is composed of luminal and glandular epithelial cells [1, 2]. Any damage to the endothelial layer may disrupt the process of implantation and may lead to endometriosis (Fig. 1) [3–5].

Endometriosis can be identified by the development of tissues similar to endometrial tissues that grow outside of the uterine lining that can cause pain in the pelvic region and on a chronic basis may also lead to infertility. It usually occurs in females that are in their reproductive age, i.e., 18–54 years [6]. Although the exact factors or mechanisms behind endometriosis are still unknown, several theories have been proposed as to how its lesions arise [7]. Several symptoms arise due to endometriosis including intermenstrual bleeding, irregularity in menses (dysmenorrhea), dyschezia, dysuria, and also disruption in quality of life among patients which makes it a critical disease that needs to be dealt with [7, 8].

According to estimates, endometriosis usually is noticed in females falling between 18 and 54 years of age

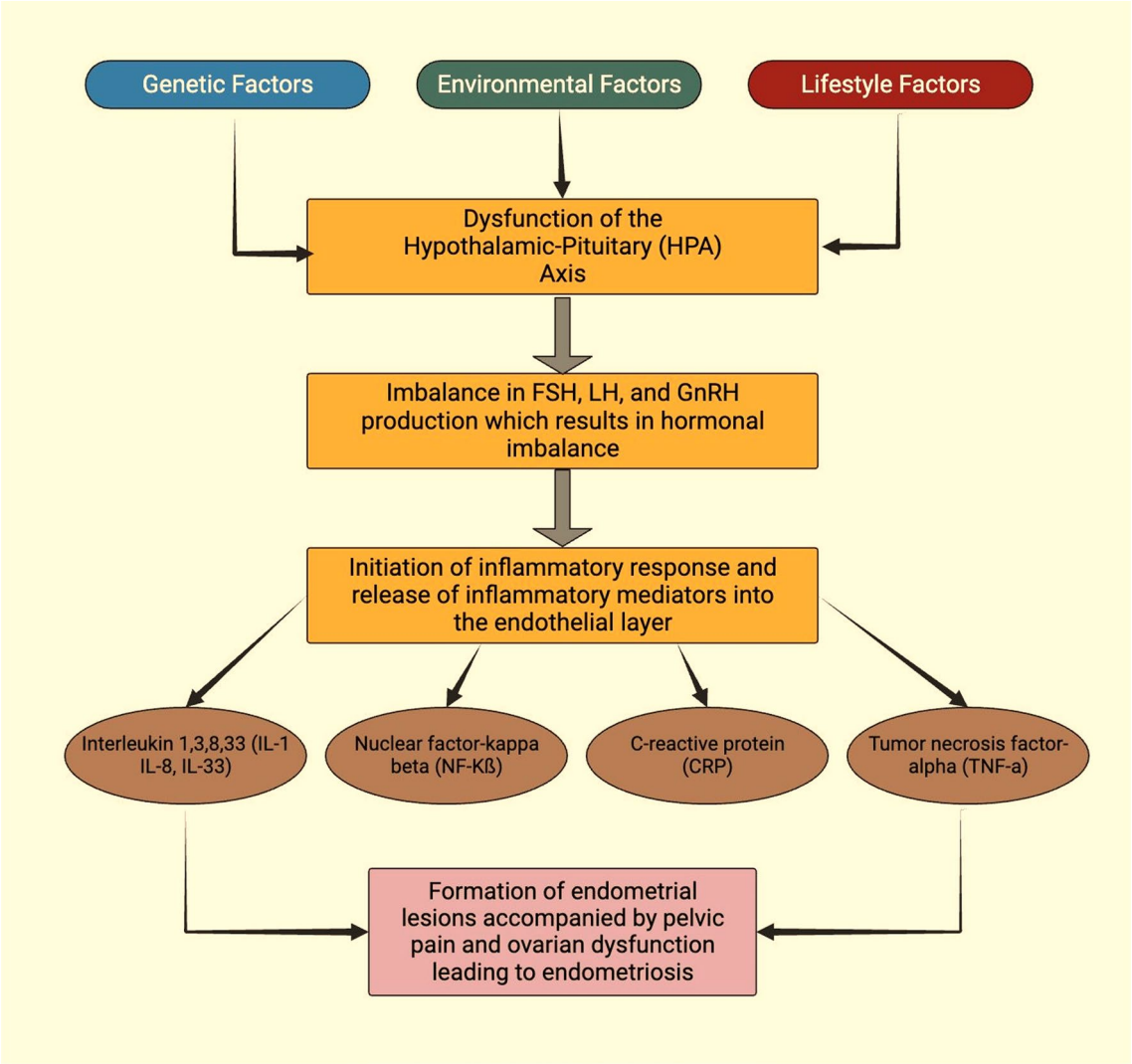

Fig. 1 An illustrative diagram representing the various factors causing endometriosis and the role of inflammation in its pathogenesis. Due to several factors including genetic, environmental, and lifestyle factors, dysfunction of the hypothalamic-pituitary axis (HPA-axis) takes place following which the production of female reproductive hormones such as LH, FSH, Anti-mullein hormone (AMH), *etc.* becomes impaired leading to an imbalance ultimately resulting in the release of inflammatory markers due to initiation process of inflammation. This can lead to damage in the endometrial layer and result in the formation of endometrial lesions resulting in pelvic pain and enlargement of the endometrium causing Endometriosis

with its proportion of incidences varying from 10 to 15% [9]. The development of this disease has been observed to take place in up to 50% of women that have experienced infertility along with 47% of adults that have undergone laparoscopic procedures at some point in their life experiencing pelvic discomfort [7]. When the race-wise risk was calculated to develop endometriosis, it was noted that the Asian women population was at the highest risk of developing endometriosis, while black women were observed to possess the highest possibility to develop endometriosis [10]. It has been observed that the prevalence of endometriosis in developed countries such as the USA, Russia, China, etc., was found to be 20% [11]. Similarly, the incidence rate of endometriosis was found to range from 34 to 48% in developing countries such as India [12]. Hormonal imbalances and their alterations can lead to elevations in the probability to develop endometriosis. Along with these menstrual factors, the early age at which menstruation commences and reduced menstrual period may also influence the likelihood of endometriosis [13–15]. Furthermore, lifestyle factors such as caffeine and alcohol intake are also associated with the development of endometriosis [16, 17]. Several factors leading to endometriosis are highlighted in Fig. 2.

The conventional therapies for the management of endometriosis include hormonal agents (norethindrone, medroxyprogesterone acetate, cyproterone acetate, dienogest), contraceptive pills (estrogen–progesterone, progestin), gonadotrophin-releasing hormone (GnRH) agonists (leuprolide, buserelin) and antagonists (cetrorelix, ganirelix), and selective estrogen receptor modulator (tamoxifen, raloxifene) [18]. Patients suffering from endometriosis are known to experience pain in their pelvic region along with abdominal pain due to which they are usually given non-steroidal anti-inflammatory drugs (NSAIDs) to relieve them from their complaints of pain and steroids to regulate inflammation occurring in the endometrial region [19–21].

The majority of therapies designed to combat endometriosis are dependent on estrogen and other hormones as they constitute a majority of the disease's etiopathogenesis [22]. However, there are certain limitations of conventional therapy used in endometriosis such as risk of recurrences, safety and efficacy issues, risk of development of adverse events, etc. [23–25].

Due to the toxic effects of synthetic drugs, more attention has been shifted toward medicinal herbal drugs to cope with the harmful side effects of conventional therapy in various gynecological disorders. Herbal drugs have emerged as a more reliable source for the discovery of novel therapeutic approaches for endometriosis [26]. They target several mechanisms associated with endometriosis such as inflammatory markers, estrogen receptors, growth factors responsible for the angiogenesis of endometrial tissues, etc. The herb Epigallocatechin Gallate (EGCG) was shown to reduce inflammation by suppressing the release of NF-κB along with mitogen-activated protein kinase 1 (MAPK-1) in the endometrial lesions [27]. Similarly, Curcumin and Ginsenoside Rg3 can inhibit the effects of vascular endothelial-derived

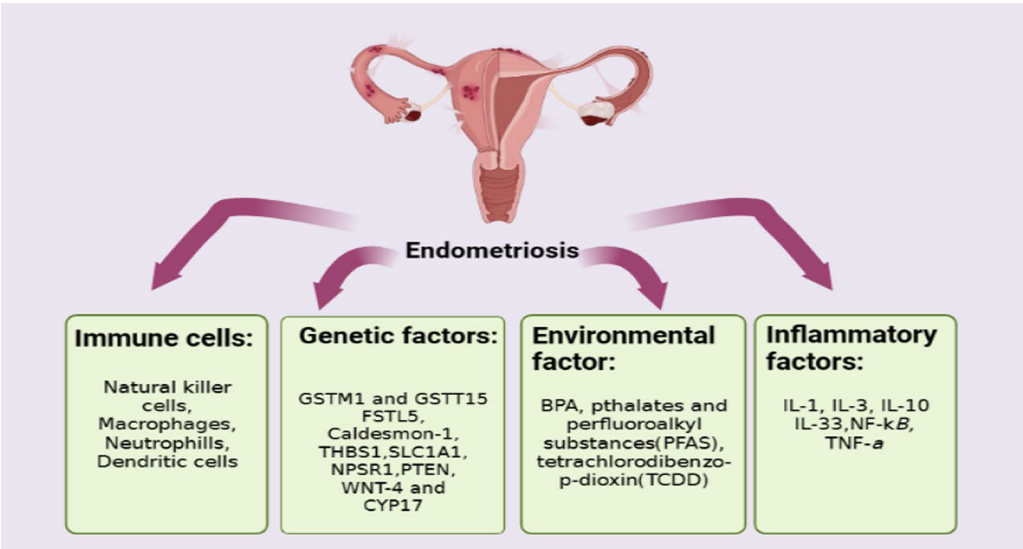

Fig. 2 Factors leading to endometriosis. Several factors may lead to endometriosis that include Genetic susceptibility towards particular genes, Immunological factors such as the stimulation of certain immune cells comprising Natural Killer cells, *etc.,* Environmental factors such as exposure to some trigger chemicals and lastly the activation of inflammatory markers such as Interleukins (IL-1,3), NF-κβ, and TNF-α

growth factor (VEGF) necessary for angiogenesis of the endometrial lining in rats suggesting their potency in endometriosis [28]. Furthermore, Curcumin, Ginsenoside Rg3**,** Resveratrol, Apegenin**, and** β-Caryophyllene decrease the levels of IL-6, IL-8, and NF-κB in human endometrial stromal cells. Also, Puerarin, Resveratrol, Curcumin, Ginsenoside Rg3, Genistein, and Herbal decoction method have been shown to attach to estrogenic receptors and compete with 17β-estradiol (E2), thereby inhibiting the production of estrogen. Their probable mechanism in endometriosis is to suppress the vascularization of the endometrial cells by targeting estrogen as it blocks the synthesis of estrogen through repression of the expression of aromatase cytochrome P450 (p450arom) in the endothelial stromal tissues as shown in Fig. 3 [29–32].

The present review compares conventional and herbal therapy based on literature evidences with the objective to identify prospective novel targets in the treatment of endometriosis. A literature search was conducted through an electronic database (PubMed, Medline, Clinicaltrials.gov, etc.) up to September 2023. The

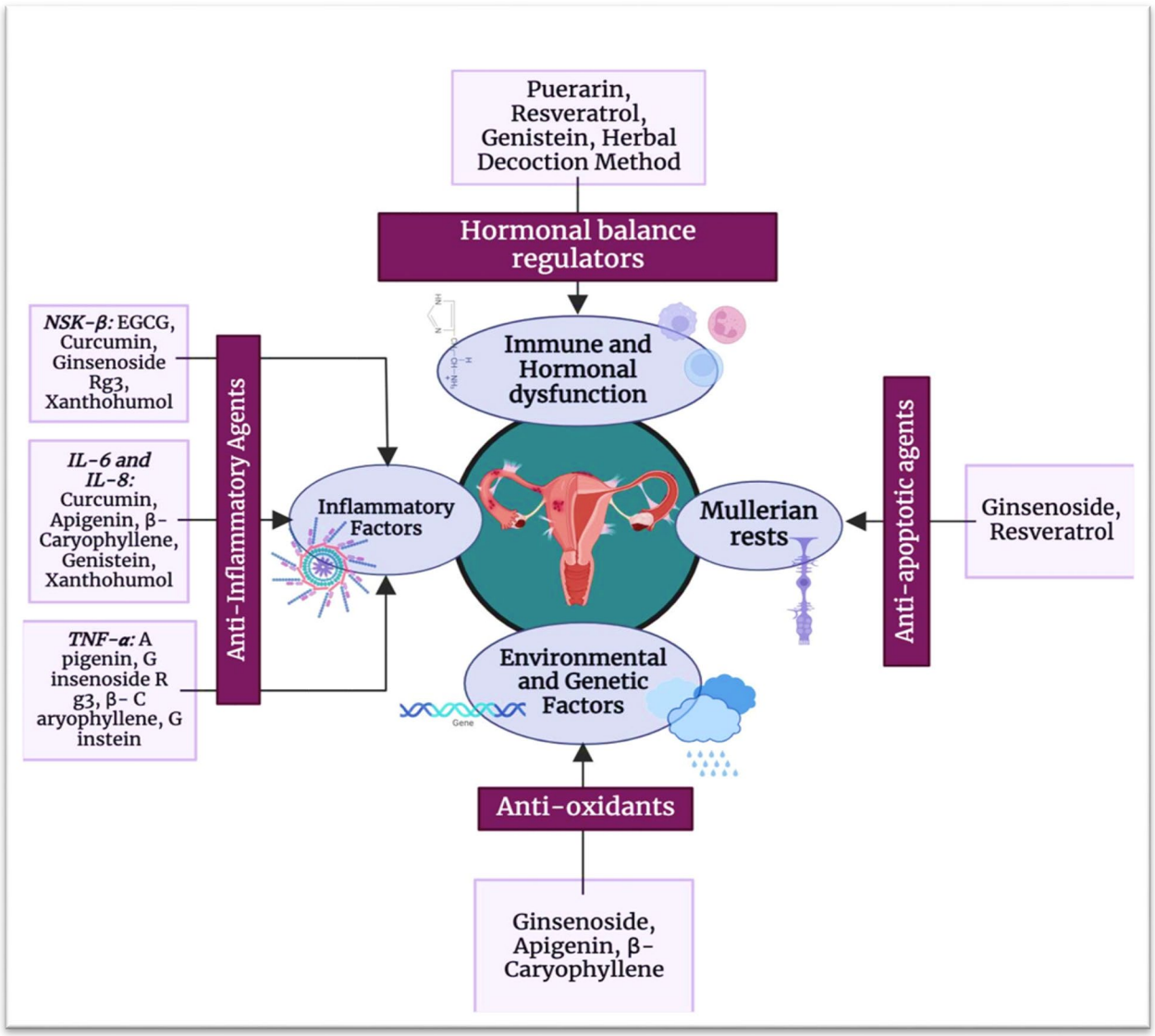

Fig. 3 An illustration representing the various sites at which herbs act in lowering the progression of endometriosis. Several traditional herbs possess many properties through which they can influence the progression of endometriosis such as Anti-oxidative (Ginsenoside, Apigenin, β-Caryophyllene), Anti-inflammatory (EGCG, Ginsenoside Rg3, Xanthohumol, Geinstein), Hormone regulatory effects (Puerin, Resveratrol, Genistein), and Anti-apoptotic effects (Ginsenoside). These herbs can work individually or in combination to treat the underlying causes of Endometriosis

following key words were entered for search strategy: Endometriosis, Conventional therapy, GnRH agonist, Estrogens, Progestins, Selective estrogen receptor modulators (SERMs), Non-steroidal anti-inflammatory drugs (NSAIDs), Herbal therapy, Traditional medicine, Genistein, Curcumin, Ginsenoside Rg3, Herbal decoction method, Puerarin, Resveratrol, etc. Literature sources were assessed based on this search strategy and included into the present review. Additionally, it gives insights into the various conventional therapy used for endometriosis along with their limitations and whether herbal medicine have any benefits over conventional therapies.

Main Text

Conventional therapy for endometriosis

Estrogen–progestins and progestins

Also termed combined hormonal contraceptives (CHCs), they are given to the patients in the form of combined pills containing both estrogen and progesterone to balance the levels of female reproductive hormones. These pills are being administered to patients with endometriosis for a long time [33]. Both hormones possess their individual properties in lowering the damaging effects of endometriosis on the female body. Estradiol has the unique characteristics of anti-apoptosis and anti-inflammatory properties which can lower the amount of the inflammation process occurring at the endometrium, while progesterone also possesses anti-inflammatory properties but promotes apoptosis. Estradiol has the unique characteristics of anti-apoptosis and anti-inflammatory properties which can lower the amount of the inflammation process occurring at the endometrium while progesterone also possesses anti-inflammatory properties but promotes apoptosis [34]. Moreover, they lessen or stop menstruation entirely, which limits the number of endometrial cells that reflux into the tubules. These pills contain a higher level of progestin while having a low level of estrogen. They are involved with regularizing the menstrual cycle. As a result of this, it would lead to a delay in the inflammation process and oxidative stress occurring within the endometrial layer [35]. There have been several investigations that have been conducted in this context, and it has been reported that about two-thirds of the female population have benefitted from estrogen–progestin therapy and their dysmenorrhea also got corrected [33, 36–38]. Certain examples of progesterone include medroxyprogesterone, norethisterone acetate, desogestrel, etc. [39].

Gonadotrophin-releasing hormone (GnRH) agonists and antagonists

The mechanism behind GnRH analogues is that they cause the pituitary gonadotrophs to be stimulated and further promote the release of follicle-stimulating hormone (FSH), luteinizing hormone (LH), etc., thereby maintaining the normal female reproductive system function and the endometrial lining [40]. An effective strategy to combat endometriosis includes the withdrawal of the hormone (estrogen) which can be provided by administering GnRH agonist. However, a higher estrogen withdrawal may result in unpredicted adverse events including bone density loss, altered mental status, and risk for cardiovascular disorders which can lead to osteoporosis [33, 41]. Elagolix is a common drug included within the category of GnRH agonists and is used for endometriosis and it has shown significant results under clinical investigations [42]. The utilization of GnRH antagonists in a similar manner to GnRH agonists has also been evaluated in endometriosis. On evaluation, it was observed that treatment with GnRH antagonists like Cetrorelix, Abarelix, and Ozarelix can ensure the successful inhibition of gonadotrophins while also maintaining the levels of estrogen in the body. Due to this, the adverse events noted with GnRH agonists can be reduced along with the progression of the disease [41]. Hence, endometriosis now has a new avenue for medical treatment due to the administration of Cetrorelix which is an GnRH antagonist.

Progestins

Another promising avenue for the treatment of endometriosis includes therapy with progesterone-only pills which are available in the market in several dosage forms such as transdermal patches, oral pills, intrauterine devices, etc. They have been associated with alleviation in pain and irregularity in menses along with limiting the size of the endometrial lesion [43]. They may act through various mechanisms such as inhibiting angiogenesis around the endometrial lining, inhibiting aromatase enzyme, catalyzing anovulation, modulating estrogen receptors, and decreasing the expression of 17β-HSD1 (hydroxysteroid dehydrogenase) [44]. Examples of progestins include medroxyprogesterone acetate, norethindrone, cyproterone acetate, lynesterole, etc. [45, 46]

Selective estrogen receptor modulators (SERMs) and selective progesterone receptor modulators (SPRMs)

These agents can attach themselves to estrogen or progesterone receptors and modulate their function resulting in modulating their signaling pathway. Due to this, the menstrual cycle gets restored due to regained balance between the estrogen and progesterone hormone levels. Certain examples of SERMs include tamoxifen, raloxifene, bazedoxifene, etc., while of SPRMs include mifepristone, asoprisnil, lonaprisan, etc. [43, 47, 48]. However, there is no hormonal therapy for endometriosis

that is free from adverse events and a therapy should be designed in such a way that it doesn't influence the normal menstrual cycle of the body in any way and subsequently leads to endometrial lesion size reduction thereby decreasing the inflammation process occurring within it.

Non-steroidal anti-inflammatory drugs

As discussed above, inflammation is an important constituent in the development of endometriosis due to the release of prostaglandins and this ultimately leads to pain in the patient [49]. Due to this complaint of pain experienced by the patients, NSAIDs can be prescribed as a supplemental therapy to relieve the patients from their pain symptoms [46]. Drugs such as mefenamic acid, naproxen sodium, ketoprofen, and ibuprofen at doses of 400 to 600 mg in the form of oral tablets for the duration of 6 to 9 months [19, 50].

Figure 4 shows a brief timeline for the development of various drugs used as conventional therapies to treat endometriosis along with their mechanisms of action.

Shortcomings of conventional therapy in Endometriosis

Conventional therapy for endometriosis has been shown to possess certain drawbacks which include:

Tolerability issues

There have been instances wherein the current treatment options for endometriosis (majorly hormonal agents) have not been successfully tolerated. Estrogen and progestins can be given in the form of combined oral contraceptives (COCs) to balance the hormonal levels of the body. However, they are associated with several adverse events due to which their tolerability decreases in patients [24]. Certain examples of adverse events of estrogens include vaginal bleeding and itching, irregular menstruation, menstrual bleeding, gastric disturbances, hot flushes, mood swings, etc. [33]. Almost all therapeutics of endometriosis have safety and tolerability issues which is why they need to be checked in patients before giving it on a chronic basis [33]. Similar to estrogen, progestins are also associated with adverse events such as hirsutism, acne, mood alterations, and weight gain [43].

Safety and efficacy issues

In some studies, it has been found that when monotherapy is given to patients suffering from endometriosis, there has not been the achievement of successful therapeutic outcomes. In an clinical investigation performed by Giudice et al., they observed that monotherapy with Relugolix is not to be given for chronic use [25]. Additionally, Barbara and colleagues evaluated the safety and efficacy of GnRH agonists in endometriosis and observed that on a long-term basis, GnRH monotherapy cannot be administered to endometriosis patients it was not found to be safe for them due to the development of severe adverse events such as weight gain, hot flushes mood swings which were frequently noticed in patients [33]. In terms of oral progestins, conventional therapy has been linked to the development of various major adverse events such as neoplasms, malignancy, endocrine abnormalities, mental and behavioral disorders, and

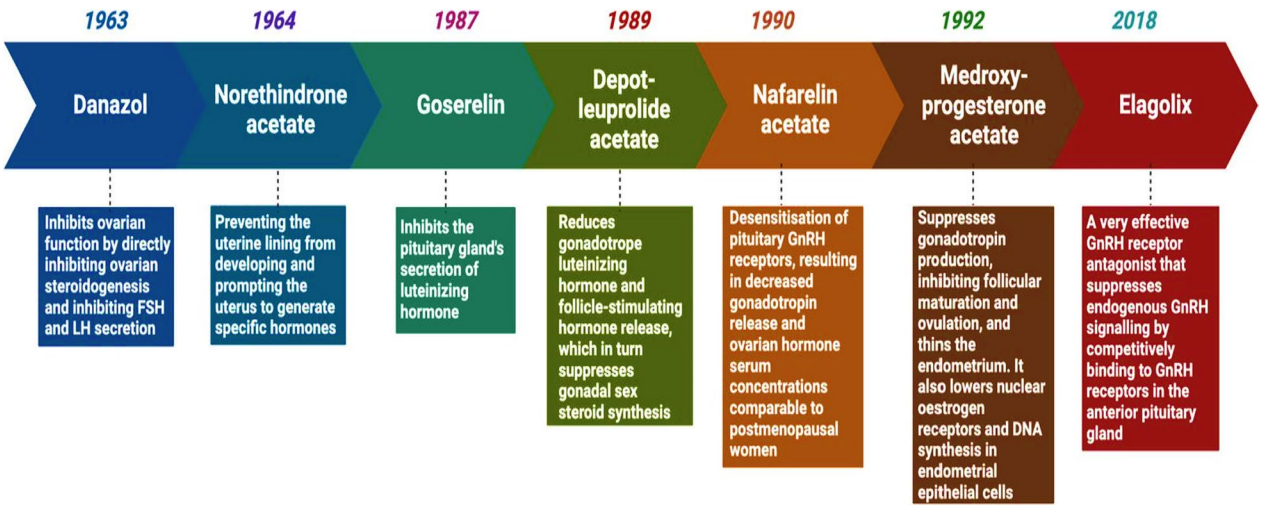

Fig. 4 A diagram representing the timeline for the development of therapeutics employed in endometriosis treatment. This figure shows a timely development of the conventional agents for endometriosis in a progressive manner. The conventional agents comprise Anti-androgens (Danazol), Progestins (Norethindrone acetate, Medroxyprogesterone acetate), GnRH antagonists (Elagolix), GnRH agonists (Gosrelin, Leuprolide, Nafrelin). The year of authorization along with their mechanisms in endometriosis has been provided in the above figure

many more. The SAE incidence rate per 10,000 women-years was 3.67% in long-term oral progestin users (treatment for more than 15 months) and 4.16% in short-term users (therapy for less than 15 months) which is why patients receiving conventional therapies are more prone to develop adverse drug reactions (ADRs) [51]. Due to the limited efficacy and safety of the conventional treatments, the patient ultimately has to undergo surgical procedures such as laparoscopy, hysterectomy, etc. [45, 52].

Cost issues

Treating endometriosis poses a substantial economic burden on the patients with the costs of therapy. This is the reason why an emphasis must be made on the cost of the therapy given in endometriosis [53]. In a study carried out by Soliman et al. wherein they evaluated the total direct costs and incremental costs between endometriosis patient and non-endometriosis control groups, they found a significant difference in both and concluded that there is a significant incremental cost to be paid in endometriosis treatment as high as $10,002 and $2132 for direct and indirect incremental costs [54]. Also, the adverse events incurred during the course of endometriosis and due to its treatment, such as pelvic pain, infertility, irregular menses, and mood swings add up to the incremental cost that the patient has to pay to deal with these complications [55].

Risk of recurrences

The greatest risk that the currently available treatments pose is the risk of recurrence of the disease due to the limited efficacy of the drugs. In most cases, the reason behind this recurrence is the presence of residual lesions or from de novo cells [23]. It was observed that the recurrence rates of endometriosis were 40–50% at a 5-year interval and 21–23% at the end of 2 years. In addition to this, the precise risk factors leading to the recurrence of endometriosis have not been identified yet [56]. Recurrence of endometriosis has also been observed in post-operative patients who have undergone surgical procedures for endometriosis [56]. Thus, it is necessary to control the recurrences of endometriosis to ensure better therapeutic outcomes in patients.

Clinical trial data of conventional therapy in endometriosis

Completed clinical trials

A list of completed clinical studies and trials for endometriosis patients and their findings are provided in Table 1. Certain examples of landmark clinical trials assessing the potency of conventional therapy in endometriosis are given below.

In a Phase-I randomized, multicentric trial performed to assess the efficacy and safety of Aromatase inhibitors (Anastrozole) and Progestin against Placebo in patients suffering from Endometriosis, 309 participants were recruited (NCT02203331). They were divided into four cohorts, (a) participants receiving Progestin (Levonorgestrel), (b) participants receiving Anastrozole in combination with levonorgestrel, (c) participants receiving leuprolide, and (d) participants receiving Placebo for the duration of 12 weeks. It was observed that all the drugs led to an improvement in the mean duration of endometriosis-associated pelvic pain (EAPP) which led to a reduction in the days that patient presented with pelvic pain [57].

In a similar Phase III study involving 815 participants, the potency of Elagolix was determined in patients suffering from Moderate to Severe endometriosis induced pain. The participants were divided into three cohorts: (a) patients receiving Elagolix 150 mg QD for a duration of 6 months, (b) patients receiving Elagolix 200 mg 4 times in a day for 6 months, and (c) patients receiving Placebo drug for a 6-month duration. It was observed after the treatment duration that Elagolix both lower and higher dose resulted in improvements in endometriosis-associated pelvic pain; however, adverse events such as hot flushes, increased serum lipid levels, increase in bone mineral density (BMD) was observed. Therefore, it was concluded that conventional therapy, although effective led to the development of adverse events in patients of endometriosis [42].

Suspended or terminated clinical trials

There have been certain instances wherein patients suffering from endometriosis were administered conventional therapy led to the termination or suspension of the clinical trial due to certain complications occurring due to the conventional agents. An example of such trial includes a study in which 50 participants were enrolled who were clinically diagnosed with endometriosis and were divided into two groups: (a) receiving Dienogest 2 mg per day and (b) receiving Levonorgestrel (0.10 mg per day) in combination with ethinyl estradiol (0.02 mg per day) [62] are progestins which reduce endometrial lining thickness thus decreasing the chance of bleeding in patients of endometriosis [63]. The outcomes measured included the change in size of the endometrial lesions from their baseline observed via ultrasound within a time duration of 1 year. It was observed that Busrelin acetate which is a GnRH agonist was equally effective in treating endometriosis as Dienogest which is why these 2 drugs were given optionally to the patients. A significant improvement in the symptoms experienced by the patients and their pain score was observed with patients that were administered Dienogest. It also led to lower reduction in bone mineral

Table 1 A table showing the various completed clinical trials for conventional therapy in endometriosis

Phase	Study design	No of participants	Eligibility criteria	Arms of the study	Study findings	Inference	Study
Phase IV	A randomized, parallel, open-label study to determine whether endometrial implantation markers predict embryo transfer fertilization outcomes in vitro in subjects already administered leuprolide acetate	37 participants	Infertility patients, diagnosis of endometriosis patients, patients who have regular menses, normal ovarian reserve testing	Intervention: Leuprolide acetate in depot suspension 3.75 mg intramuscular every 28 days	The study found that there were no significant differences for outcomes such as rate of fertilization, stimulation of gonadotrophin hormones, etc. A high rate of fertilization rates was observed in the group of patients who were administered GnRH regimen which led to a larger frequency of implantations within them	It was concluded from this study that GnRH agonist administration in endometriosis can lead to an increase in the rates of pregnancies in comparison to the conventional ovarian stimulation techniques	Surrey et al. [58]
Phase II	A randomized parallel-assignment study to observe the efficacy of hormonal therapy in combination with GnRH agonist in patients suffering from endometriosis	53 participants	Women aged 13–22 years, body weight between 18 and 30 kg/m^2, surgical diagnosis of endometriosis, willing to comply with study requirements	Intervention: Norethindrone acetate 5 mg orally + Conjugated equine estrogens 0.625 mg orally Control: Norethindrone acetate 5 mg + placebo capsule 1 pill daily	At 12 months, the intervention group increased the bone mineral density (BMD) and the overall mineral content of the body, while the control group did not show these outcomes. Quality-of-life assessments showed greater improvements in physical functioning with the interventional group. There were no significant adverse events were reported	Add-back therapy with norethindrone acetate led to preservation of the skeletal health in endometriosis patients, the combination of norethindrone acetate and conjugated equine estrogens being led to higher elevations in the BMD of the body. The therapy was safe and effective, with no tolerability issues	DiVasta et al. [59]
Phase II	A randomized, parallel-assignment pilot study to determine the effect of dopamine receptor agonist therapy for pain relief in women suffering from endometriosis	10 participants	Women with confirmed case of endometriosis, age between 15 and 40 years	Intervention 1: Cabergoline (0.5 mg PO two times a week for 6 months duration) Intervention 2: Norethindrone acetate (5 mg po daily for 6 months)	It was observed from this study that many subjects taking cabergoline experienced a decrease in pain scores and improvement in pain complaints compared to subjects treated with Norethindrone acetate. Cabergoline was also well tolerated by the patients	It was concluded that Cabergoline could be a safe and effective therapeutic alternative for chronic pain in endometriosis resistant to standard care, according to a pilot study. Larger randomized trials are needed to confirm these findings	DiVasta et al. [60]

Table 1 (continued)

Phase	Study design	No of participants	Eligibility criteria	Arms of the study	Study findings	Inference	Study
Phase not applicable	A prospective, randomized, parallel-assignment clinical trial to study the effect of administration of GnRH agonist before in vitro fertilization to observe fertilization rate and pregnancy rate in endometriosis patients	180 participants	Patients with infertility, endometriosis stage 1	Intervention: Leuprolide (single injection of 3.75 mg every 28 days) Procedure: In vitro fertilization (IVF)	The use of GnRH agonist resulted in a decrease in Follicular fluid cytokines in women compared to those who did not receive this regimen. However, no significant improvement took place in terms of embryo quality, rate of implantation, or rate of pregnancy	Low follicular fluid cytokine levels along with high rates of implantations were noticed in subjects receiving GnRH agonist for the duration of 3 months, with no significant difference in pregnancy and implantation rate	Kaponis et al. [61]

density (BMD) as compared to Busrelin acetate. However, compared to Busrelin acetate, a higher instance of genital bleeding and hot flushes within these patients was noticed with Dienogest highlighting its concern. This was the reason due to which this trial had to be suspended to avoid complications in these patients [62]. Due to the safety concerns occurring in conventional agents, it leads to negative therapeutic effects and it has been proposed that they be monitored carefully during treatment and if they pose any risk to the patients, the trial should be terminated immediately. Also, novel drugs which are safer and more tolerable by the patients are required to prevent complications from occurring in them.

Herbal therapy for endometriosis

Epigallocatechin Gallate (EGCG)

Epigallocatechin-3-gallate (EGCG) is the main constituent of green tea due to which it can display its potency in cancer and endometriosis [64]. This herb has already been shown to possess anticancer and anti-oxidative properties. However, its effects in endometriosis were also evaluated by several researchers in endometriosis. It was shown to reduce inflammation by suppressing the release of NF-κB along with mitogen-activated protein kinase 1 (MAPK-1) in the endometrial lesions [55]. However, sufficient investigations have not been carried out as of yet to underline the exact mechanisms of EGCG through which it can cure endometriosis. The preclinical testing of EGCG in endometriosis was done by Ricci and co-workers in which they observed that treatment with EGCG inhibited the development of endometrial lesions along with decreasing the size of their lesions. It was able to modulate cellular proliferation, decrease the blood circulation to and from the endometrial lesions, and enhance the process of apoptosis [65].

Curcumin

It is the active ingredient of commonly occurring turmeric which has anti-inflammatory, anti-oxidative, and anti-proliferative properties [26, 66]. It can also block the actions of vascular endothelial-derived growth factor (VEGF) within the endometrial cells of the rats suggesting its effects as anti-angiogenetic agents as VEGF is crucial for endometrial blood vessels to grow further and proliferate [58]. Furthermore, it is able to decrease the levels of IL-6, IL-8, and NF-κB in human endometrial stromal cells (Fig. 4). Hence due to all these beneficial properties, it has been suggested that curcumin may also be employed as a potential therapeutic agent for endometriosis [26].

Ginsenoside Rg3

This is a Chinese traditional herb and is the active component of ginseng which originates from the plant genus Panax. Preclinical findings have revealed the ability of this herb in reducing the endometrial lesion size in rats [67]. Its main actions include anti-oxidative and anti-inflammatory activities [26, 59]. In addition to this, this herb can also repress the angiogenesis process by inhibiting the VEGF-mediated formation of blood vessels suggesting its efficacy in reducing endometriosis [60]. Furthermore, a study carried out by Huang et al. found that Ginsenoside Rg3 reduced inflammation by repression of NF-κB and TNF-α in ectopic endometrial cells and also modulated apoptosis by regulating the expression of caspase 3 and inhibiting VEGF-mediated angiogenesis [68].

Puerarin

It is the major active ingredient of Gegen which is extracted from the Chinese medical herb Radix puerariae and falls in the category of phytoestrogens but possesses a weak estrogenic effect. They have sown to attach to estrogenic receptors and compete with 17β-estradiol (E2) thereby inhibiting the production of estrogen (Fig. 4). Its probable mechanism in endometriosis is its ability to suppress the vascularization of the endometrial cells by estrogen as it blocks the synthesis of estrogen through repression of the expression of aromatase cytochrome P450 (p450arom) in the endothelial stromal tissues [62–65]. When preclinical analysis was carried out, it suggested that it could influence and inhibit the inflammatory microenvironment of the endometrial tissue in rats [32].

Resveratrol

Resveratrol is also a phytoestrogen that is derived from grapes, wine, peanuts, etc. It has been identified to act against the progression of endometriosis due to its effects of anti-inflammation, via the repression of prostaglandin synthesis along with the modulation of apoptosis [69]. It has the ability to influence the estrogenic receptors (ER1 and 2) and has a mixed mechanism of action i.e., agonist and antagonist [67]. In addition to this, it has also been shown to regulate various pathways associated with cellular maturation and death such as MAPK, protein kinase B (Akt), protein kinase C, and peroxisome proliferator activated receptor-gamma (PPAR-ϒ) [70–72].

Apigenin

Apigenin belongs to the category of flavonoids and is found in parsley, celery, oranges, wheat sources, etc. It possesses, anti-inflammatory, anti-proliferative, and

anti-oxidant properties [73, 74]. Suou et al. in a study to undermine the effects of apigenin in endometriosis observed that it reduced inflammation via suppressing protein expression and regulating the levels of IL-8 and TNF-α (Fig. 4) [75]. Recently conducted studies also revealed its effect in acting through binding with the progesterone receptors (PR) behaving as a probable phyto-progestin [76]. It was also shown to correct endometriosis symptoms such as pelvic pain, dysmenorrhea, infertility, etc. [77].

β-Caryophyllene

It belongs to the category of sesquiterpenes and is the active ingredient of essential oils which are derived from spices and food plants and is an effective anti-inflammatory herb in vivo and was found to correct endometrial symptoms and infertility in adult rats [78, 79]. It was shown to mediate the inflammatory response by regulating their markers such as IL-1β, TNF-α, and toll-like receptors-4 (TLR-4) and angiogenesis by VEGF regulation. Recent findings also suggest its ability to block the generation of ROS through the MAPK pathway [74, 80].

Genistein

It is an iso-flavonoid which is extracted from soy. It has strong Phyto-estrogenic actions and has been demonstrated both in vivo and in vitro and has been indicated in the treatment for endometriosis [81]. Genistein was shown to limit the progression of endometrial carcinoma in adult women as it regulated the process of angiogenesis within the endometrium and apoptosis [82]. Additionally, it can modulate the estrogenic receptors (ER) to regulate the release of estrogen and the process of angiogenesis occurring due to it. Furthermore, it can regulate inflammation by mediating the release of IL-6 and TNF-α [81].

Xanthohumol

It is the active ingredient of *Humulus lupulus* L. and possesses a variety of actions including anti-angiogenetic, anti-inflammatory, and anti-proliferative effects. Inflammatory mediators such as NK-κβ, IL-1, Akt etc. can be regulated due to this herb [74, 83].

Herbal decoction method

These methods are commonly employed in China to treat a variety of gynecological disorders such as endometriosis since 1983 [84]. Certain examples of these methods include Qu Yi Kang (QYK), Yi Wei San (YWS), Xiaochaihu decoction (XCHD), Huoxue Xiaoyi (HX), and Xuefu Zhuyu (XZD) decoction methods based on their inventors [84]. Investigations into this have shown that XZD may relieve the symptoms of endometriosis, such as dysmenorrhea and ectopic lesions, and improve the issues of infertility in women and has resulted in greater efficacy of about 90% in the past times [84, 85]. Furthermore, XCHD has been shown to reduce the levels of estradiol (E2) levels, aromatase enzymes and also modulate the inflammatory mediator synthesis through the blockade of the COX-2 enzyme [85]. Other methods of decoction include Cai Shi Nei Yi Fang, Neiyi Zhitong, Huazhuo Jiedu Huoxue, and Juan Tong Yin etc.[86].

In a study carried out by Ding et al. involving 80 patients wherein they compared the effects of Chinese traditional medicine and hormonal therapy (12.5 mg mifepristone orally each day) for Endometriosis. They observed that Chinese traditional medicine had a greater pregnancy rate (52.5%, 21/40) than hormonal therapy (37.5%, 15/40) within a 12-month period of follow-up and equivalent therapeutic effect to hormonal therapy suggesting a better potency of herbal therapy. Moreover, there were no SAE's associated with herbal therapy and the results of renal and hepatic profile parameters proved that herbal therapy was well tolerated by all the patients [87]. This proves the long-standing efficacy as well as safety of herbal medicine to treat Endometriosis.

Additionally, Zhao et al. carried out a study in which they compared the effects of Chinese herbal medicine and western medicine by the means of a randomized controlled trial in 208 patients (106 in Chinese herbal medicine group and 102 in the western medicine group). Patients in the western medicine group were treated with a GnRH agonist or gestrinone, whereas patients in the Chinese medicine group were treated with agents including Modified Guifu Decoction, Radix Aconiti lateralis Preparata, Ramulus Cinnamomi, Radix Linderae, Rhizoma Sparganii, Rhizoma Curcumae, Spina Gleditsia, Radix Salviae Miltiorrhizae, etc. For the patients in the Chinese medicine group, the mean time following surgery to achieve the first pregnancy was significantly shorter than for the patients in the Western medicine group ($t = -2.09$; $P = 0.04$). A statistically significant difference existed between the 2 groups in terms of safety observed as after the treatment follow-up period, the western medicine group had increased ADRs such as fever, sweating, colpoxerosis, hypaphrodisia, weight gain, insomnia, irregular bleeding, headache, acne, and bone pain, while the patients in the Chinese medicine group only complained of occasional stomach pain that was immediately lowered after modifying the herbal remedies and dosages (83.3% vs. 9.4%, $P < 0.01$) [88].

Herbal combination therapies were associated with improving pregnancy rates, reducing adverse events and inhibiting the growth of endometrial tissues in addition to decreasing inflammation in patients. Therefore, combination therapy comprising of certain herbs may prove

to be beneficial in treating Endometriosis compared to conventional therapies. Furthermore, they have shown improvements in sub-populations of endometriosis patients including infertility patients, pre-menopausal syndromes, menstrual cycle irregularities, autoimmune disorders, etc. in terms of better hormonal balance restorations, ovulation induction, lowering inflammation proving their efficacy. The major herbal agents discussed in the present review such as curcumin, EGCG, Genistein, β-Caryophyllene, etc., have shown limited adverse events in comparison with conventional therapy in terms of gastric disturbances including diarrhea, stomach upset, gastric irritation, etc. which can be easily managed with supportive treatment thereby enhancing their safety profile. In addition to this, their low cost of therapy adds to their benefit in treating Endometriosis.

Herbal therapy has evolved over the recent times due to their offered advantages in the studies discussed above and other factors such as low cost, ease of convenience of preparing, reduced side effects and increased bioavailability. However, several additional investigations and clinical trials need to be conducted to evaluate efficacy and safety of different combinations of herbal therapies in Endometriosis which may also lead to the discovery of novel therapeutics to combat the disease effectively.

Preclinical and clinical trial data of Herbal novel therapy in endometriosis

The current ongoing preclinical trials in which the investigations into the effects of herbal medicine to treat endometriosis are carried out are highlighted in Table 2.

Preclinical trials

Completed clinical trials

There are a relatively limited number of clinical studies carried out to evaluate the safety as well as efficacy of herbal medicine against endometriosis. Phase-I randomized, placebo-controlled trial was carried out in 185 participants to gain idea on the potency of green tea extract in endometriosis in which the effects of green tea or Epigallocatechin-3-gallate were compared with a placebo in order to assess its response. The investigators found that green tea extract displayed anti-angiogenetic, anti-fibrotic, and anti-proliferative properties which led to beneficial outcomes in lowering the progression of endometriosis and was tolerable by the patients suggesting its importance [91].

Similarly, a relatively same type of clinical trial was performed to evaluate the potency of garlic in endometriosis. A total of 120 participants were recruited and one cohort was administered garlic tablets, while the other was given a placebo after which the response toward therapy was observed. It was noted that the patients that were receiving garlic therapy showed improvements in pain and statistical tests also showed its significance which concluded that herbal therapy can provide symptomatic relief also in addition to preventing the course of progression of endometriosis [92].

Ongoing clinical trials

Table 3 enlists the various investigations that are presently ongoing to investigate the effects of herbal therapy in endometriosis.

Future prospects and opportunities

Up till now, the treatments under existence only aim to regulate the hormonal levels in the body and provide relief from symptoms of endometriosis such as pain, dryness, infertility, etc. However, no specific treatments are available that can cure endometriosis completely or reduce its course of progression into its more severe forms. They only aim to suppress ovulation or alter the levels of hormones such as estrogen and progesterone in the body. Thus, there is a need to develop individualized regimens pertaining to specific patients to lower the incidences and recurrences of endometriosis [93]. Therefore, herbal medicines can prove to be a means to develop novel therapeutics to be given to endometriosis patients as many drugs have shown potent effects in decreasing the size of endometrial lesions and reducing inflammation within them [81]. Herbal drugs are pleiotropic agents meaning they have multiple mechanisms of actions such as anti-oxidative anti-inflammatory, anti-angiogenetic, estrogen-modulating, analgesic, etc., which could resolve pelvic pain complaints of the patient along with lowering endometrial inflammation by blocking the release of inflammatory markers and protection from ROS species. By this, they can act as curative as well as symptomatic relief-providing agents [94]. Also, the improved safety and tolerability profile along with reduced cost of therapy makes them beneficial candidates over the conventionally available drugs presently in the market [84, 95]. Furthermore, recent data suggests that medicinal cannabis as a dietary intervention may have effects in treating Endometriosis as it acts through various mechanisms such as suppressing inflammation, alleviating bloating, and acting as a painkiller. However, it has not fully been studied and additional research into this can be fruitful [96, 97]. Herbal therapy can also be used to induce pregnancy in an individual who cannot conceive due to endometriosis and can be utilized as a safer approach compared to conventionally existing drugs with almost no harm to the individual or the fetus [98]. Only further and larger number of studies need to be conducted in a similar manner to evaluate the extent of the benefit that herbal therapy provides or reducing the likelihood of developing

Table 2 A table showing the animal preclinical trials conducted to evaluate the potency of herbal medicine in endometriosis

Sr. No	Study objectives	Study design	Arms of the study	Study findings	Study
1	A study in order to find the association between the Ginsenoside Rg3 effect on endometrial growth and the PI3K/Akt/mTOR signaling pathway modulated by VEGFR-2	The rats were allocated on the basis of randomization into 5 groups which were treated with ginsenoside Rg3 and sacrificed 21 days post drug treatment. Measurement of the endometrial volume was carried out and the inhibitory rate was calculated. Serum estradiol (E2) and progesterone (P) levels were analyzed by Electrochemiluminescence Immunoassay (ECLI). Using immunohistochemical techniques, the protein expression of VEGF and VEGFR-2 was evaluated within the endometrium	Intervention 1: Ginsenoside Rg3 (5 mg/kgBW/d) Intervention 2: Ginsenoside Rg3 (10 mg/kgBW/d) Intervention 3: Gestrinone group (0.5 mg/kgBW/d) Intervention 4: Control group (10 mL/kg BW/d of 0.5% Carboxymethyl cellulose sodium) CMC-Na Intervention 5: Ovariectomized group (10 mL/kgBW/d of 0.5%CMC-Na)	It was observed that a dose-dependent suppression of endometrium size in rats in comparison to control group occurred. A down-regulation of the expression of VEGF and VEGFR-2 was also noticed in Ginsenoside Rg3 group	Cao et al. [67]
2	A study to evaluate the effect of EGCG in mice-model of endometriosis	The potential for EGCG as an anti-angiogenesis agent was investigated in mice suffering from endometriosis. Transplantation of endometrium was done in mice and they were divided into 3 groups to receive treatment for 4 weeks. Endometrial growth was measured through non-invasive in vivo imaging (IVIS). Post-treatment, the bioavailability, anti-oxidative and anti-angiogenesis effects were measured	Intervention 1: Dulbecco phosphate buffered saline Intervention 2: Vitamin E (20 mg/kg) Intervention 3: EGCG (50 mg/kg)	A significant reduction in the endometrial lesion size was observed in the group treated with EGCG from 2nd to 4th week of drug treatment. However, they failed to show effect on Ovarian follicles and uterine endometrial glands	Xu et al. [89]
3	A study to investigate the potency of puerarin in endometriosis (EMT) model rats and to find the probable mechanisms of action	The animals were allocated into 5 groups and endometriosis was induced surgically by auto-transplantation of endometrial tissues. Serum estradiol (E2) and prostaglandin E2 (PGE2) levels were analyzed and the dose of administration was calculated. Genes and proteins of the endometrial tissues were analyzed by polymerase chain reaction (PCR) and immunohistochemistry (IHC). Based on the results, appropriate inferences were made	Puerarin and Raloxifene (RLX) both mixed with CMC prorata after which the animals were allocated into five groups were respectively administered drug treatment for 4 weeks Intervention 1: low-dose group (0.1% CMC and 5 mg/kg puerarin) Intervention 2: 0.1% CMC and 20 mg/kg puerarin) Intervention 3: 0.1% CMC and 80 mg/kg puerarin) Intervention 4: positive control group (Raloxifene hydrochloride) RLX 10 mg/kg Intervention 5: Control group (CMC)	It was observed that Puerarin reduced the concentrations of E2 and PGE2 and also hindered the maturation of endometrium tissues by inhibiting the expression of aromatase cytochrome P450 (p450arom) and cyclooxygenase-2 (COX-2). Also, it modulated the metabolism of E2 by controlling the expression of the 17β-hydroxysteroid-2 (17β-hsd-2) enzyme of the endometrial tissues	Surrey et al. [58]

Table 2 (continued)

Sr. No	Study objectives	Study design	Arms of the study	Study findings	Study
4	A clinical study to assess the effect of β-caryophyllene on endometriosis along with fertility status in adult female rats along with their roles in reproduction	Fragments of endometrium were implanted in the peritoneal cavity of the animals to induce endometriosis within them. Their growth was measured from baseline and after 4 weeks. Allocation was carried out of the animals into 2 groups and they were given drug therapy for a duration of 21 days	Intervention: β-caryophyllene (10 mg/kg or 30 mg/kg) Control: Vehicle	It was observed that β-Caryophyllene was able to hinder the maturation of endometriotic tissues 52.5% in rats compared with controls whereas β-caryophyllene led to apoptosis in the epithelium of the endometrial lesions	Abbas et al. [90]

Table 3 Currently ongoing clinical studies for the evaluation of herbal therapy in endometriosis

NCT number, current phase	Study design	Eligibility criteria	Arms of the study	Primary endpoints
NCT04493476, Phase II	A double-blind, prospective and placebo-regulated clinical trial to assess the response of combination therapy of Chinese herbal medicine and curcumin to lower the symptoms of endometriosis	Women having a confirmed diagnosis of endometriosis, women aged 18–45 years (reproductive age), no allergy to the ingredients of the intervention or the control	Intervention: Daily dietary dosing of Chinese medicine and curcumin given in the form of 800 mg capsules Control: Placebo (Invo capsules given in daily dosing)	The overall benefit in the symptoms of the disease
NCT03016039	A randomized, parallel assignment study of curcumin supplementation for endometriosis	Age above 18, patient with a diagnosis of pelvic inflammatory disease/ Tubo ovarian abscess, surgical wound infection, endometritis	Intervention: Curcumin supplementation	Change in the Levels of C-reactive protein, change in the levels of white blood cells
NCT03875261, Phase II	A randomized, single-group assignment study to examine the response of the effect of Cannabinoid (CBD) on pain experienced by endometriosis patients	Women falling in the age group of 18 and 40, having a confirmed diagnosis of endometriosis with clinical investigations, suffering from symptoms of pain, dysmenorrhea, etc.	Intervention: Participants administered cannabinoid derivates dosing between 1 and 12 puffs. Each puff contained 2–7 mg of delta-9-tetrahydrocannabinoland 2–5 mg of cannabidiol	Pressure threshold in hypogastrium that induces pain
NCT02676713, Phase II	A randomized, prospective, multicentric study to evaluate the efficacy of Decoction (Chinese herbal medicine to treat infertility) in endometriosis	Women having a clinical diagnosis of endometriosis, endometriosis fertility index (EFI) score greater than 4 points, firstly undergoing laparoscopic surgery, the female of reproductive age (18–45 years)	Intervention: Decoction **(**Bupleurum 10 g, Cyperus 10 g, Salvia miltiorrhiza 20 g, Red peony 10 g, etc.) Placebo: Combination of maltodextrin, lactose, edible pigment, and taste masking agent	Pregnancy rate to an extent of six menstrual cycles
NCT04150406, Current phase not given	A multicentric, randomized clinical trial to evaluate the potency of Flexofytol in endometriosis	Women of reproductive age (18–51 years), diagnosed with endometriosis, moderate to severe pelvic pain	Intervention: Flexofytol (Curcumin 42 mg 2 capsules administered for 4 months) Control: Placebo	Alteration in the baseline pain score
NCT number not given	A randomized, multicentric clinical trial to evaluate the effect of Ashokarishta, Ashwagandha Churna, and Praval Pishti in patients suffering from menopausal syndrome	Females of age 40–55 years, suffering from amenorrhea for a period of greater than 12 months, were willing to comply with the study requirements, providing written consent to be included in the study	Intervention: *Ashokarishta* (25 mL *daily*), *Ashwagandha* (3 g *twice daily with milk*), *Praval Pishti* (250 mg *twice daily*) Control: Placebo	Improvement in the Menopausal rating scale (MRS), Incidences of adverse events (AEs)

endometriosis and curing it completely. Herbal therapy trials were limited in number, while trials for conventional therapy were found to be widely available. Therefore, when the results of trials for herbal therapy become available, they will strengthen the point discussed in this manuscript regarding the comparison of safety and efficacy of conventional and herbal medicine.

Conclusion

The currently existing conventional therapies are only aimed at inhibiting the hormonal parameters of the patient and providing symptomatic relief from symptoms such as pelvic pain, vaginal dryness, etc., but cannot completely cure the disease. Conventional therapy also possesses several other limitations such as increased cost of therapy, risk of recurrence of endometriosis, limited safety and efficacy profile, and tolerability issues. On the other hand, herbal therapies extracted from natural sources have shown promising effects in delaying the course of endometriosis progression and have better effects compared to conventional therapy along with improved tolerability and almost no adverse events to the patients making them a perfect candidate for the treatment of endometriosis concerning to efficacy, safety, and tolerability. The comprehensive studies data indicate that conventional therapy results in unsatisfactory therapeutic outcomes, disease recurrence, and an increase in the development of ADRs, whereas herbal combination therapy acts through multiple mechanisms, resulting in better clinical therapeutic outcomes and less ADRs, highlighting their benefit in terms of efficacy and safety in treating endometriosis. However, the number of preclinical and clinical trials investigations into this context is limited which is why additional studies are crucial to identify the potency of herbal drugs treating endometriosis effectively.

Abbreviations

17β-HSD1	17-Beta hydroxysteroid dehydrogenase
ADRs	Adverse drug reactions
AEs	Adverse events
Akt	Protein kinase B
AMH	Anti-mullein hormone
BMD	Bone mineral density
BPA	Bisphenol-A
CBD	Cannabinoid
CHCs	Combined hormonal contraceptives
CMC-Na	Carboxymethyl cellulose sodium
COCs	Combined oral contraceptives
CRP	C-reactive protein
E2	17β-Estradiol
ECLI	Electrochemiluminescence Immunoassay
EFI	Endometriosis fertility index
EGCG	Epigallocatechin Gallate
EMT	Endometriosis model rats
ER1 and ER2	Estrogenic receptors 1 and 2
FSH	Follicle-stimulating hormone
GnRH	Gonadotrophin-releasing hormone
HPA	Hypothalamic-pituitary axis
HX	Huoxue Xiaoyi
IHC	Immunohistochemistry
IL	Interleukin
IVF	In vitro fertilization
IVIS	Non-invasive in vivo imaging
LH	Luteinizing hormone
MAPK-1	Mitogen-activated protein kinase-1
MRS	Menopausal rating scale
NF-κβ	Nuclear factor-kappa beta
NSAIDs	Non-steroidal anti-inflammatory drugs
P450arom	Aromatase cytochrome P450
PCR	Polymerase chain reaction
PGE2	Prostaglandin E2
PKC	Protein kinase C
PPAR-ϒ	Peroxisome proliferator activated receptor-gamma
PR	Progesterone receptors
QOL	Quality of life
QYK	Qu Yi Kang
RLX	Raloxifene hydrochloride
SAE	Serious adverse events
SERMs	Selective estrogen receptor modulators
SPRMs	Selective progesterone receptor modulators
TLR-4	Toll-like receptors-4
TNF-α	Tumor necrosis factor-alpha
USA	United States of America
VEGF	Vascular endothelial-derived growth factor
XCHD	Xiaochaihu decoction
XZD	Xuefu Zhuyu
YWS	Yi Wei San

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Author contributions

BD, SB, HR and MS contributed to manuscript first draft preparation and subsequent editing, literature and data collection, data analysis, figures and diagram conception as well as designing and writing the manuscript. AK and NP contributed to topic conception, design of content and skeleton, manuscript draft review and editing, figures and diagram conception, overall monitoring, and guidance throughout the study duration. All authors have read and approved the final manuscript.

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Not applicable.

Consent for publication

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Competing interests
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