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REVIEW ARTICLE

Novel Drug Targets with Traditional Herbal Medicines for Overcoming Endometriosis

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Abstract: Endometriosis is a disease in which the lining of the endometrium is found outside of the uterus. Recent medical treatments for endometriosis have adverse effects, limiting their long-term use. Furthermore, the recurrence of the disease after the cessation of therapy is quite common, and most patients need to continue treatment to maintain a hypoestrogenic environment till conception. Notwithstanding recent advances in computational and chemical practices, traditional medicines are considered the most consistent sources for the discovery of new drugs. Numerous medicinal plants and plant-derived compounds have been tested against gynecological disorders, mainly endometriosis. This review aimed to describe the pharmacological activity profile of the medicinal plants and their active ingredients and draw attention to the discovery of multitargeted drug molecules for rational therapy.

Keywords: Endometriosis, plants, phytochemicals, endometrium, cervix, glandular-cystic hyperplasia.

1. WHAT IS ENDOMETRIOSIS?

Endometriosis is a chronic inflammatory disease in which the lining of the endometrium is found outside of the uterus. A uterine fibroid originates from the smooth muscle layer of the uterus. Early pregnancy loss may be caused by mechanical obstruction of implantation or distortion of the cervix or endometrium [1-3]. It is generally characterized by pathological lesions, endometritis, pyometra, and glandular-cystic hyperplasia, and diagnosed based on the patient's histological findings [4].

2. ETIOLOGY AND PATHOGENESIS OF ENDOMETRIOSIS

The etiology and pathogenesis of endometriosis remain unclear. It may be caused by coelomic metaplasia, retrograde menstruation or both [3, 5, 6]. It involves a complex interplay of genetic, anatomic, immunologic, and environmental factors [7-10]. Intense macrophage infiltration and excess cytokine expression have a crucial role in the progression of endometriosis-related chronic inflammation [7, 11, 12]. Endometriotic implant nidation involves remodeling of the local peritoneal atmosphere facilitated by extracellular matrix-degrading proteases [13, 14]. Matrix metalloproteinases (MMPs) have a leading role in such tissue remodeling. Endometriotic lesions show the increased expression of MMP-1, MMP-3, and MMP-7 [15, 16].

Endometriosis can be associated with pain at ovulation, including cyclic pelvic pain, severe dysmenorrhea, deep dyspareunia, dysuria, and dyschezia (painful bowel movements) [1, 17-21]. Endometriosis-associated pain can be caused by peritoneal inflammation, adhesion formation, and specific innervation of endometriotic lesions. It correlates with the presence of deep infiltrating disease [22-25]. Endometriosis can appear as peritoneal lesions, ovarian superficial implants or endometriotic cysts, and/or deeply infiltrative disease with extension to bowel, bladder, and ureter. It is often associated with pelvic adhesions [26].

Hormonally stimulated cyclical bleeding from the endometriotic deposit may contribute to the induction of a local inflammatory reaction and fibrous adhesion. It may result in an endometrioma or chocolate cyst in the case of deep implants in the ovary [27]. Endometrial implants cause cellular and molecular variations. Ectopic implants respond to estrogen and progesterone, and a series of immunomodulators, inflammatory mediators, and proteins involved in oxidative progression enduring the last phases of the menstrual cycle are produced [28, 29]. An increase in the number of inflammatory cells and the production of inflammatory cytokines, can cause pelvic inflammation owing to local and systemic responses of the immune system [30, 31]. Growth factors and inflammatory mediators secreted by peritoneal leukocytes are involved in the pathogenesis of the disease through an increase in the number of endometrial cells at ectopic

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sites, whereas a large number of inflammatory cells and mediators, such as proteolytic enzymes, peritoneal macrophages, complement fragments, prostaglandins (PG), IL-1, and tumor necrosis factor (TNF), are produced in the peritoneal fluid of patients suffering from the disease [32].

3. DIAGNOSIS OF ENDOMETRIOSIS

The diagnosis of the disease can not be based merely on physical examination and patient history. The only reliable method is a laparoscopic inspection of the peritoneal cavity [33, 34]. A noninvasive assessment for endometriosis is valuable for the early detection of endometriosis in symptomatic women who have pelvic pain and/or subfertility with normal ultrasound outcomes. This includes all patients with minimal-to-mild endometriosis, patients with moderate-to-severe endometriosis deprived of a clearly observable ovarian endometrioma, and patients with pelvic adhesions and/or other pelvic pathology that may progress into pelvic pain and/or subfertility. This improves the diagnostic performance of noninvasive or semi-invasive tests for endometriosis, with panels of identified peripheral blood biomarkers, protein markers revealed by miRNA, proteomics, and endometrial nerve fiber density. Trials with high sensitivity and suitable specificity have been established; some have been confirmed in self-determining populations and are consequently promising. For actual improvement, international agreement on promoting biobanking is required for standard operating processes for the collection, treatment, storage, and analysis of tissue samples and for complete clinical phenotyping of these samples. Additionally, it is compulsory to confirm the diagnostic precision of any suitable test prospectively in a self-determining symptomatic patient population with subfertility and/or pain deprived of clear ultrasound suggestion of endometriosis and with a clinical sign for surgery, assorted into patients with laparoscopically and histologically established endometriosis and controls with the laparoscopically established absence of endometriosis.

Earlier studies focused on adhesion molecules, inflammatory and noninflammatory cytokines, angiogenic and growth factors, and glycoproteins, found to be highly related to the pathogenesis of endometriosis and the development of endometriotic lesions. Nevertheless, neither a single biomarker nor a panel of biomarkers has been confirmed as a consistent noninvasive test for endometriosis [35]. Cancer antigen 125 (CA-125), the most extensively examined and generally used peripheral biomarker of endometriosis [36], is produced by endometrial and mesothelial cells. It enters into the circulation through the endothelial lining of capillaries in response to inflammation. CA-125 levels in the peripheral blood lack diagnostic power as a single biomarker of endometriosis owing to low sensitivity [37, 38]. Previous studies showed that the levels of cytokines, growth and angiogenic factors as well as tumor markers improved in the peripheral blood of women with endometriosis compared with controls [35, 39]. However, none of them, alone or in combination, have been confirmed as a noninvasive test for endometriosis [35]. This may be because most studies were performed on a small number of patients with an incomplete assessment of different phases of the menstrual cycle and endometriosis, incomplete statistical analysis, and evaluation of only a few biomarkers. Owing to the different types and locations of endometriosis, it is likely that a dissimilar subset of biomarkers might be essential for the diagnosis of dissimilar stages of endometriosis [5]. That is, women with peritoneal endometriosis might have unlike markers compared with those with rectovaginal endometriosis [35].

Vascular Endothelial Growth Factor (VEGF), one of the key stimuli for angiogenesis and improved vessel permeability, contributes to the advancement of endometriotic lesions [40, 41]. However, no consensus exists concerning the significance of VEGF as a biomarker of endometriosis. The VEGF level in the peripheral blood is improved [42-44] in women with endometriosis compared with controls possibly owing to variances in study design and methodology [45-47]. Glycodelin, an endometrium-derived protein with identified angiogenic, contraceptive and immunosuppressive, properties may contribute to the progression of endometriosis and endometriosis-related infertility [48]. Furthermore, glycodelin is not only produced in the glandular epithelium of secretory endometrium [49, 50] but also released from endometriotic lesions into the peritoneal fluid and serum [48, 50, 51]. Improved glycodelin levels in plasma have been observed in patients through endometriosis [50, 51]. Soluble intercellular adhesion molecule-1, one of the main adhesion molecules that inhibit natural killer cell-mediated cytotoxicity is involved in the implantation and progression of endometriotic lesions [52, 53]. Annexin V, a marker of apoptosis, has been found to be a promising semi-invasive endometrial biomarker for the diagnosis of minimal-to-mild endometriosis [54]. Actually, alterations in the regulation of apoptosis in the eutopic and ectopic endometrium of women with endometriosis may contribute to the persistence of endometrial cells in the peritoneal cavity and the advancement of endometriosis [55]. Presently, no consensus exists concerning the value of inflammatory factors as biomarkers of endometriosis. TNF-α, IL-1 [46, 56, 57], IL-6 [56, 57], and IL-8 [56, 58] levels are improved in women with and without endometriosis. Previous studies showed that the levels of TNF-α [44, 59], IL-6 [46, 59], IL-8 [60, 61], and interferon-g (IFN-g) [46] increased in the peripheral blood of patients with endometriosis compared with controls.

An increasing body of evidence indicates that endometriosis may be diagnosed on the basis of an increased number of nerve fibers in the endometrium of women with endometriosis compared with controls [62-65]. The immunohistochemical analysis showed that sensory nerve fibers were present in the functional layer of human endometrium, leading to the production of several neural transmitters, for example, vasoactive intestinal polypeptide, substance P, and neural proteins such as neuropeptide Y, calcitonin gene-related protein, protein gene product 9.5, and neurofilament [64]. A higher number of small unmyelinated nerve fibers have been observed in the functional layer of endometrium in women with definite endometriosis compared with those without endometriosis [65, 66]. However, other studies showed that the occurrence of nerve fibers in the functional layer of endometrium does not rely on the occurrence of endometriosis but is related to the diagnosis of pelvic pain [67-69]. Additionally, comparable endometrial innervation and neurotrophin-3 and nerve growth factor expression have been described in women with adenomyosis without endometriosis and in women with mutual adenomyosis and en-

dometriosis, which needs to be confirmed through large-sample studies [67].

Mild endometriosis may also vary the environment of the uterus and affect ovulation, hormones, and even a newly-formed embryo. It can cause damage to the fallopian tubes, leading to blockage and hindering ovulation or collection of the ovum. This is accompanied by chronic inflammation, fibrosis, adhesions, and ovarian cyst formations, ultimately leading to malignant disease if not treated [70].

4. TREATMENT OF ENDOMETRIOSIS

Treatment of endometriosis-associated symptoms requires surgical and medical intervention [71]. Although the available medical treatments are not completely therapeutic, they are a mainstay of pain suppression and reversion of lesions in women suffering from the disease.

The treatments are based on blocking the secretion of estrogen from ovaries, Oral contraceptives and progestins or danazol and Gonadotropin-Releasing Hormone agonists (GnRH-a) are used the treatment of endometriosis, to relieve short-term levels symptoms [2, 72, 73]. The short-term benefits of these treatments should be evaluated together with the harmful side effects that may result. Meanwhile, continuous use of oral contraceptives has been found to increase the risk of thromboembolism in some patients, for example, smokers aged more than 35 years or those who have a history of cardiovascular disease, and women trying to conceive [74]. Danazol can cause androgenic changes, for instance, acne, weight gain, and menopausal symptoms, such as hot flushes and fatigue. Previous studies have indicated its possible role in increasing low-density lipoprotein cholesterol levels and its conceivable involvement in ovarian cancer [2, 75]. GnRH-a generally decreases estrogen levels more than danazol, and its menopausal side effects, such as insomnia, hot flushes, reduced libido, and vaginal dryness are more severe [2]. Reduced estrogen levels can also lead to serious osteoporosis. The long-term adverse effects of add-back regimes, which use small quantities of progesterone and estrogen, have not yet been completely explored. Patients using progestin treatment suffer more from bloating, acne, spotting, and fluid retention. Progestin may affect the level of high-density lipoproteins in the blood, possibly enhancing the risk of cardiovascular side effects, such as thrombosis [76].

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) are characteristically used as the first-line treatment for pain because they have fewer side effects. Continuous efforts have been made to discover new drugs with higher efficacy, fewer side effects, and possible long-term treatment for those suffering from severe endometriosis [77]. These agents include aromatase inhibitors [78], thiazolidinediones [79], cyclooxygenase (COX)-2 selective NSAIDs [80], selective progesterone receptor modulators [81], MMP-inhibitors [82], recombinant human TNF-α binding proteins [83], anti-VEGF therapy [84] and interferon (IFN)-alpha-2b [85].

Preclinical trials have shown that the beneficial effects of these drugs may be attributed to their antiproliferative, anti-inflammatory, or antiangiogenic properties. Although many therapeutic options are available, effective long-term treatments are really required [86].

Surgical management of endometriosis-associated symptoms consists of laparoscopic ablation, pelvic anatomy restoration, and hysterectomy. In approximately 50% of these patients, symptoms have recurred by the time of their 1-year follow-up. The aforementioned therapeutic strategies can not generally resolve all the symptoms [31].

Recent medical treatments for endometriosis have adverse effects, limiting their long-term use. Furthermore, the recurrence of the disease after the termination of treatment is quite common. Consequently, it is essential to look for more safe and effective long-term treatments.

Currently, natural compounds present in diet and plants are being explored for treating various diseases, such as cancer, which parts significant likenesses with endometriosis although the concluding is a benign disease [87].

5. IMPORTANCE OF FOODS AS A TREATMENT FOR ENDOMETRIOSIS

Endometriosis progresses naturally in some women, although most find that their symptoms last or progressively degenerate. Dietary treatment of endometriosis is based on the statement that estrogen is involved in the progression of endometriosis. The cells do not grow if the body is deprived of estrogen. This indicates that the dietary components that decrease the estrogen levels can be used to treat endometriosis [88, 89]. Diet modification to deal with endometriosis is an exceptional way to resolve the symptoms. Adjustments in diet can help in addressing several progressive physical and metabolic alterations. Several diseases and illnesses have responded positively to changes in diet, and endometriosis is no exception [90]. Changing diet for endometriosis may help reduce pain, cramps, inflammation, bloating, estrogen levels, weight, and toxins. An improved diet also increases energy levels, boosts immune system, and improves overall health [91, 92].

Since a large proportion of body's immune system originates from the digestive tract, a healthy digestive system is essential for an effective immune system. A healthy gut and a healthy digestive system aid in the production of good bacteria, enzymes, and vitamins that help fight diseases [93, 94]. Having a strong and vibrant immune system helps fight the original causes of endometriosis. The body is sensitive to food allergies or too much sugar or caffeine in the diet [95]. Occasionally these sensitivities have certain signs and symptoms, but if they are not perceived in time, they result in nutritional deficiencies and ill health. However, the body gives indications and demands improvements in diet [96].

The promoting effect of certain food groups on endometriosis is based on the chemical reactions in the body influenced by these food groups. Some of these chemical reactions are subtle and multifaceted based on enzymes in food and the complex reactions to the chemicals already present in the body [97, 98].

A controlled diet helps inhibit these chemical reactions and reduce various symptoms of the disease. An appropriate diet can help balance the levels of different forms of estrogen [99]. Prostaglandins are complex natural fatty acids derived from dietary sources. They have different forms, and new forms are still being discovered. They are also responsible

for painful menstrual cramps and the pain during endometriosis. A change in diet can change the level and types of prostaglandins in the body. The diet to treat endometriosis is aimed to block the prostaglandins having negative effects on the body and increase the levels of prostaglandins that have positive effects. Prostaglandins having negative effects increase uterine contractions, pain, and inflammation. On the contrary, prostaglandins having positive effects are soothing [100, 101]. A change in the oil content of the diet can promote the activity of good prostaglandins [102, 103]. The good oils belong to the omega-3 fatty acid group; they are responsible for the production of good prostaglandins. Some of the best sources of omega-3 oils are pumpkin seeds, oily fish, walnut oil and dark green leafy vegetables [104-106]. At the same time, it is important to decrease the consumption of the fatty acids that stimulate the production of bad prostaglandins, which are found in saturated fats, animal fats, and butter [107].

6. IMPORTANCE OF MEDICINAL PLANTS USED IN FOLK MEDICINE TO TREAT ENDOMETRIOSIS

Natural products have become a significant part of human health care system owing to the side effects and toxicity of synthetic drugs [108]. Nearly 80% of the world population use traditional therapies for primary health care. Furthermore, several modern pharmaceuticals used to treat illnesses in people and animals are based on plants [109]. Nearly 70% of medicines are derived from natural sources [110]. Native information from tribals has been an important tool in screening new medicinal plants for use [111]. The traditional information has turned into principles underlying various phytochemical, pharmacological, and clinical studies, leading to novel drug discovery and development [110]. The scientists are involved in ethnomedicinal researches based on the valuable information from the tribal societies in recent years. Folkloric information about the use of medicinal plants has accepted and approved by different generations [112].

Medicinal plants and botanical products are now commonly used for managing the symptoms of numerous gynecologic disorders, for instance, endometriosis. Medicinal plants and their active compounds have displayed antiproliferative, antioxidant, analgesic, and anti-inflammatory properties. These properties may help in treating or regressing endometriosis [113, 114].

Pain is the most serious concern in this illness, and therefore its management has great significance. Herbal painkillers for the pelvis and abdomen can be used individually or in combination. These herbs include *Cimicifuga racemosa* (L.) Nutt. (Ranunculaceae), *Viburnum prunifolium* L. (Caprifoliaceae) and *Viburnum opulus* L. (Adoxaceae), *Matricaria chamomilla* L. (Asteraceae), *Corydalis* sp. (Papaveraceae), *Pulsatilla* sp. (Ranunculaceae), *Angelica sinensis* (Oliv.) Diels (Apiaceae), *Zingiber officinale* Roscoe (Zingiberaceae), and *Piscidia piscipula* (L.) Sarg. (Fabaceae). *Corydalis* and *Pulsatilla* are used mainly in the thoughtful management of pain; the latter is specifically used against ovarian pain. Antispasmodics, such as *Dioscorea villosa* L. (Dioscoreaceae), black haw, black cohosh, chamomile, and ginger are generally used for cramps, sharp and dull pains, and drawing pains in the lower back and thighs. Antispasmodics and anti-inflammatory agents, for instance, wild yam, viburnum, ginger, and chamomile, can be used to treat uterine, intestinal, bowel, and urinary pain and irritability; the pain of endometriosis originates from the irritation of endometrial tissue outside of its normal site in the uterus. Sedatives are active when deep rest or sleep provides relief from pain [32, 115].

Patients who have immunological complications together with symptoms of endometriosis may need immunostimulation to support their immune response; also, herbs, such as *Echinacea* sp. (Asteraceae), *Astragalus* sp. (Fabaceae), or *Picrorhiza kurroa* Royle ex Benth. (Plantaginaceae) in combination with adaptogens such as *Withania somnifera* (L.) Dunal (Solanaceae), *Panax quinquefolius* L. (Araliaceae), *Rhaponticum* sp. (Asteraceae), or *Rhodiola rosea* L. (Crassulaceae) may be beneficial in such cases. Medicinal fungi, such as *Ganoderma lucidum* (Curtis) P. Karst (Ganodermataceae) and *Cordyceps* (Clavicipitaceae), might also provide support to the immune systems of patients. Hyperimmunity and atopic situations, such as eczema or chronic rhinitis, or autoimmunity, can be treated with immunosupportive anti-inflammatory adaptogens, such as *Glycyrrhiza glabra* L. (Fabaceae), ashwagandha, and American ginseng. Whether immunostimulating herbs, such as *Echinacea* sp. and *Astragalus* sp., are suitable for use in the case of autoimmunity is still unclear. Adaptogens concurrently influence and restore the functions of the immune system and the hypothalamic-pituitary-adrenal axis, both of which are affected by the illness. The endometrium is composed of glandular tissue scattered with endometrial stroma, similar to lymphoid tissue. Therefore, herbal therapies conventionally used to recover lymphatic circulation, such as *Calendula* sp. (Asteraceae), *Echinacea* sp., *Galium aparine* L. (Rubiaceae), and *Phytolacca* sp. (Phytolaccaceae), are frequently used to treat endometriosis [32, 115].

7. EXPERIMENTAL STUDIES ON MEDICINAL PLANTS AGAINST ENDOMETRIOSIS

In vitro and *in vivo* experimental studies on the medicinal plants traditionally used for treating endometriosis are presented in the following sections according to the family names of the plants in alphabetic order.

7.1. Acanthaceae

Andrographis paniculata (Burm.f.) Wall. ex Nees has been used for the treating infections and some diseases. Andrographolide, labdane diterpenoid, was isolated from the stem and leaves of this plant. This compound showed antitumor activity and inhibited tumor angiogenesis. It has been considered that those properties of the compound could be due to its NF-κB inhibitor activity. According to previous studies, andrographolide was proven to decrease endometriotic lesion volume and improve in generalized hyperalgesia in an endometriosis rat model. This effect was mediated via COX-2, tissue factor and the phosphorylation of p50 and p65 (Table **1**) [116, 117].

7.2. Adoxaceae

The fruits of *Viburnum opulus* L. are used for the treating gynecological disorders such as primary and secondary dysmenorrhea and ovarian cysts in folk medicine. Shade-dried and grinded fruits of *V. opulus* were extracted with *n*-

and grinded fruits of *V. opulus* were extracted with *n*-hexane, ethyl acetate (EtOAc), and methanol (MeOH), respectively and the activities of the prepared extracts were investigated on the surgically-induced endometriosis rat model. In this model, adhesion scores of endometriotic implants, endometriotic foci areas and cytokine levels of the peritoneal fluids were examined. According to the results, the EtOAc extract of the plant significantly decreased adhesion scores of endometriotic implants, endometriotic foci areas and cytokine levels of the peritoneal fluids.

HPLC analyses were conducted on the EtOAc extract which is the most potent extract when compared to the other extracts to determine its chemical fingerprint. HPLC analyses exhibited that chlorogenic acid was the major compound of the EtOAc extract (Table **1**) [118].

7.3. Apiaceae

Angelica sinensis (Oliv.) Diels root "dong quai" has been used in Chinese medicine to treat "blood stasis". It has antispasmodic, analgesic, blood-enriching, blood circulating, and tonic effects, besides being an antioxidant, partly through the inhibition of anion radical formation [116]. A few studies have demonstrated its immunomodulatory and anti-inflammatory activities. It stimulates phagocytosis and IL-2 production. It exerts immunostimulatory and anti-inflammatory effects on initial and late-phase inflammation after ferulic acid is given orally [119, 120].

In a previous study, dong quai fluid extract was used to treat dysmenorrhea in nulliparous women and severe bleeding in multiparous women. It was given for 1 week before menstruation and helped reduce menstrual pain and chronic endometritis, partially by inhibiting PG synthesis and lessening inflammation (Table **1**). The *in vitro* synthesis of thromboxane A2 was also inhibited, stimulating blood circulation [121].

Centella asiatica (L.) Urban "gotu kola," is used for its anti-inflammatory and antimicrobial properties. It is considered in the cases of endometriosis, combined with other herbs, for complete treatment or to help in recovery after the surgery [32, 122].

7.4. Asteraceae

In Turkish folk medicine, the aerial parts of *Achillea* L. species are used for their emmenagogue potential [123, 124]. The role of *Achillea biebersteinii* Afan. in treating endometriosis was assessed. Experimental endometriosis was induced in 6-week old female, nonpregnant, Sprague-Dawley rats. A 15-mm piece of endometrium from uterine cornu was sutured into the abdominal wall. After 28 days, a second laparotomy was performed. The endometrial foci areas were calculated, and intra-abdominal adhesions were scored. The abdomen was closed. *n*-Hexane, ethyl acetate, and methanol extract prepared from the aerial parts of *A. biebersteinii* were administered per os once in a day throughout the study. At the end of the treatment, all rats were sacrificed. The endometriotic foci areas and intra-abdominal adhesions were again evaluated and compared with the previous findings. Moreover, the peritoneal fluid was collected to detect TNF-α, VEGF and IL-6 levels (Table **1**). Post-treatment volumes were found to be significantly decreased, and the levels of TNF-α, VEGF, and IL-6 were reduced in the ethyl acetate extract-treated group. The ethyl acetate extract of *A. biebersteinii* appears to be a promising alternative for treating endometriosis due to the flavonoid aglycones found in the extract [125].

Echinacea sp. is used as an antioxidant. It stimulates the immune system, enhances the production of phagocytes, cytokines, and immunoglobins, and reduces inflammation in women with endometriosis (Table **1**) [32, 126].

Tanacetum parthenium (L.) Sch. Bip. "feverfew" has been used as an anti-inflammatory agent. However, no studies have reported on its use to treat endometriosis. The herbal literature suggests its use as an antinociceptive and anti-inflammatory agent. It inhibits the activity of PG synthetase, which stops arachidonic acid conversion into inflammatory PGs, mast cell degranulation, and subsequent release of histamine, serotonin, and other inflammatory cytokines, such as TNF-α, IL-1, NF-κB, and IFN-g, as well as peritoneal cyclooxygenase, in animal models (Table **1**) [32, 127].

7.5. Boraginaceae

Lithospermum erythrorhizon Siebold & Zucc. possesses wound healing, antimicrobial, antiinflammatory, antitumor, and antioxidant activities. It has been considered that antitumor activity of this plant could be due to its angiogenesis inhibitory effect [128]. Shikonin is main compound of *L. erythrorhizon*. Shikonin was found to decrease the volume of human endometrial tissue in severe combined immunodeficiency mice *via* regulated upon activation normal T-cell expressed and secreted mRANTES levels in the peritoneal fluid (Table **1**) [129].

7.6. Hypericaceae

Latest fears about St. John's wort's interaction with various pharmaceutical drugs have led to a host of contraindications for its use [32]. It promotes the activity of cytochrome P450 3A4 and increases the entry of several drugs and steroids, for instance, cortisol and ethinyl estradiol. Hence, it may be used to positively interfere with estrogen binding when the estrogen levels are high in endometriosis (Table **1**). A few studies have explored its capacity to bind estrogen. Simmen *et al.* (1999) [130] showed that estrogen binding was 50% inhibited by the bioflavonoid I3, II8-biapigenin at a micromolar concentration in the central nervous system. Its use in controlling estrogen levels supports its valuable role in treating mild-to-moderate depression, which may accompany chronic endometriosis [131].

7.7. Lamiaceae

Vitex agnus-castus "chaste berry" is used to treat endometriosis, with clinical trials supporting its use for infertility initiated by luteal phase dysfunction (Table **1**). Its effects on estrogen levels are still undefined. Only one study demonstrated its estrogen-like effects; it increased uterine growth in ovariectomized rats and decreased estradiol levels. However, other studies have reported no effects, although clinical observations support its use [132, 133].

Vitex negundo Linn. "five-leaved chaste tree; horseshoe vitex; Chinese chaste tree" leaf decoction decreases the symptoms of endometriosis in clinical practice. Amuthan *et al*. [134] reported the effect of *V. negundo* aqueous extract on surgically induced endometriosis. The extract reduced the endometrial cyst size and damaged the endometrial epithelial morphology. Ethanolic extracts of the seeds of *V. negundo* exhibited estrogen-like activity, which advocated its use in hormone replacement therapy [135]. The anti-inflammatory and antioxidant activities of the plant extract have been previously confirmed (Table **1**) [136]. The drug also displays a similar effect on the intrauterine endometrium.

7.8. Malvaceae

Gossypium sp. "cotton", commonly used as a uterine tonic and to stimulate uterine contractions, has shown the short-term effectiveness of up to 90% in treating endometriosis and long-term efficacy of 54%-63% after 1-3 years. Its side effects include amenorrhea continuing for up to 6 months in 80% of women and up to 1 year in 16% of women, with 4% suffering from amenorrhea for longer than 1 year. Its active ingredient, gossypol, has been found to antagonize the effects of estrogen and progesterone (Table **1**) and mimic a pseudomenopausal state. Its side effects include hypokalemia, which is treated using slow-releasing potassium salts. High-doses can increase liver enzyme levels, nausea, edema, palpitations, rash, and fatigue; reduce appetite; and inhibit thyroid function and mitochondrial energy metabolism. This compound is not available in the West, as studies on its efficiency against endometriosis have not been approved. Consequently, it has been classified as a pharmaceutical drug in place of a herbal therapy [32, 137, 138].

7.9. Paeoniaceae

Paeonia lactiflora Pall. "white peony" has been used to treat endometriosis. The peeled root of this plant, which is also used to treat endometrial dysmenorrhea, contains an unusual cage-like monoterpene named paeoniflorin. A good-quality root contains at least 2% paeoniflorin. It displayed antispasmodic effects in the smooth muscle of the ileum and uterus in mice, rabbits, and guinea pigs when given orally in a decoction. A traditional Eastern formula containing *Paeonia* decreased the levels of the tissue-specific anti-endometrial immunoglobulin M antibody in patients with endometriosis (Table **1**). *Paeonia* may also normalize the estrogen-progesterone balance. An *in vitro* study concluded that the incubation of ovary cells with *Paeonia* led to in increased progesterone secretion. However, the research into this has yielded varied results [32, 139].

7.10. Rosaceae

Alchemilla vulgaris L. "Ladies Mantle," used conventionally for menorrhagia, has displayed progesterogenic, astringent, antihemorrhagic and anti-inflammatory properties. Antihemorrhagic herbs, which are high in tannins, also contain compounds that can affect uterine bleeding. In a study performed in Romania, a fluid extract of Ladies Mantle, given 10-15 days before the beginning of the menstrual cycle, was found to exert antihemorrhagic and prophylactic effects on adolescent girls with metrorrhagia [138, 140].

A study by Kupeli Akkol *et al.* evaluated the use of *Alchemilla mollis* (Buser) Rothm. and *Alchemilla persica* Rothm. in experimentally induced endometriosis models in rats. Endometriosis was surgically induced in rates by auto-transplanting endometrial tissue into the abdominal wall. The groups were orally treated with the aqueous methanol extracts of aerial parts and roots of *A. mollis* and *A. persica*. The cyst formation was considerably reduced using the aerial part extract of *A. mollis.* A decrease in endometrioma was likewise observed using the aerial part extract of *A. persica*. The *A. mollis* aerial part extract was also found to decrease the levels of cytokines (Table **1**). The aerial part extracts of *A. mollis* and *A. persica* might be useful in managing endometriosis. The effect might be partially attributed to their phenolic components [141].

7.11. Rubiaceae

Uncaria tomentosa (Willd. Ex Schult.) DC., "cat's claw," used to treat infections with inflammatory or oxidative stress, has anti-inflammatory and antioxidant properties. It inhibits the secretion of lipopolysaccharides, nitrites, and PGE2 and can also change cell cycle progression *via* inducing apoptosis. It inhibits the production of TNF-α, a powerful pro-inflammatory cytokine and critical mediator of chronic inflammatory states (Table **1**). It controls the expression of several pro-inflammatory cytokines, for instance, TNF-α, IL-1, IL-2, IL-6, and IL-8. Therefore, it might serve as a promising alternative for treating endometriosis [31].

7.12. Verbenaceae

A previous study investigated the effect of *Verbena hastata* L. "blue vervain" on the uterus. In a study by Wichtl (2004) [142], hot water extracts of European *Verbena* stimulated the secretion of luteinizing hormone and follicle-stimulating hormone. It also exerts anti-thyrotropic and abortifacient effects through inhibiting human chronic gonadotropin, and immunomodulatory effects by inhibiting the phagocytosis of human granulocytes (Table **1**). It is usually used to treat the fundamental causes leading to endometriosis [32].

7.13. Zingiberaceae

Zingiber officinale Roscoe "ginger" root is used as an anti-inflammatory and antispasmodic agent against several inflammatory disorders in dysmenorrhea affected by endometriosis. It is consumed as a tincture with other plant extracts. It can be used as a poultice and infused in baths for pelvic pain, although trials on these uses are lacking [32, 143].

8. PLANT CONSTITUENTS USED IN THE TREATMENT OF ENDOMETRIOSIS

8.1. Epigallocatechin Gallate

Epigallocatechin Gallate (EGCG) is a catechin monomer from green tea that has recently been shown to treat dissimilar types of cancer, including ovarian cancers, cervical cancers, and uterine leiomyoma cancers [144-152]. Not many studies have explored the ability of EGCG to inhibit the beginning of endometriosis [153, 154].

EGCG is crucial in antiangiogenesis and antioxidation. It increases apoptosis and inhibits the function of microvessels in the lesions, thus reducing the size and weight of lesions and inhibiting the growth of experimental endometriosis [155]. Moreover, EGCG selectively suppresses the expression of VEGF-C and VEGF receptor 2 and reduces extracellular regulated kinase activation in endothelial cells (Table **1**) [154]. Another study demonstrated that endometriotic lesions and glandular epithelium reduced after treatment with EGCG for 2 weeks by downregulating angiogenic VEGF A mRNA levels and upregulating NF-κB and mitogen-activated protein kinase 1 mRNA levels in lesions [156]. Laschke *et al*. found that EGCG might diminish E2-stimulated activation, proliferation, and VEGF expression in endometrial cells of rat endometriosis models, therefore inhibiting the formation of new endometriotic lesions [157].

Ricci *et al.* investigated the effect of herbal treatment with EGCG on the development of endometriotic-like lesions experimentally induced in BALB/c mice. EGCG inhibited the development of endometriotic-like lesions, reducing the size of the lesions by lessening cell proliferation and increasing apoptosis. Furthermore, the treatment decreased the number of recognized lesions per mouse. A treatment that began 15 days after the surgery affected the progression and conservation of previously recognized endometriotic-like lesions [158].

EGCG has earlier been found to exert anticancer effects [147, 152]. Some latest trials displayed its antiangiogenic effects on endometriosis [154, 156]. The antiproliferative and proapoptotic effects of EGCG on endometriosis were consistent with the findings of previous experimental trials [149, 151].

8.2. Curcumin

Curcumin is a polyphenolic monomer extract from "Turmeric" *Curcuma longa* (Zingiberaceae). It stimulates microcirculation and possesses several pharmacological activities such as antioxidant, anti-inflammatory, and antiproliferative. Curcumin and the Chinese medicine formula with turmeric might considerably improve and relieve the symptoms of endometriosis [159, 160]. Angiogenesis and new blood supply are essential for the survival of endometriosis implants attached to the peritoneum and the development of endometriosis. The peritoneal fluid of women with endometriosis has more angiogenic activity than women without the disease. The secretion of angiogenic factors into the peritoneal compartment augments the microvascularization in the peritoneum. VEGF is the most important angiogenic factor in endometriosis [161]. Several studies revealed that curcumin use reduced the number of microvessels and the protein expression of VEGF in the ectopic endometrium of rat endometriosis models; also, the mRNA expression of the TNF-α-induced cell surface and total protein expression of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 reduced (Table **1**) [160, 162]. Moreover, curcumin reduced the secretion of IL-6, IL-8, and monocyte chemotactic protein-1 (MCP-1) and inhibited the activation of transcription factor NF-κB in human endometriotic stromal cells. Other trials showed that curcumin treatment inhibited the expression and activities of MMP-2 [163], MMP-3 [164], MMP-9 [165], and VEGF [145] protein in rat endometriosis models; also, the endometriotic lesions reduced. In addition, Zhang *et al*. reported that curcumin decreased the number of endometriotic stromal cells at the concentrations of 10, 30, 50 μM in human eutopic endometriotic stromal and epithelial cells [161, 166]. Jana *et al*. (2014) exhibited to reduce the serum VEGF, MMP-2, MMP-9 levels, reactive oxygen species (ROS), microvessel density (MVD) and lipid peroxidation with the administration of curcumin [161, 167].

8.3. Puerarin

Puerarin is a major isoflavonoid compound extracted from Radix puerariae. It has a weak estrogenic effect by binding to estrogen receptors [168, 169]. Several studies showed that the weight of endometriotic tissue and the level of serum estrogen were lower in the puerarin and danazol treatment groups than in the control group in rat endometriosis models [145]. Puerarin treatment reduced the levels of MMP-9, ICAM-1, and VEGF protein (Table **1**), but increased the level of tissue inhibitor of metalloproteinase-1 (TIMP-1) in endometriotic stromal cells (ESCs) [169]. The invasion of endometriotic tissue is reliant on MMPs and TIMPs because they together are vital in the growth and decomposition of endometrium tissue. The VEGF family is important in angiogenesis, contributing to the growth and invasion of ectopic endometrium. Puerarin suppresses the invasion of ESCs and the vascularization of ectopic endometrial tissues through regulating MMP-9, ICAM1, VEGF, and TIMP-1.

8.4. Ginsenoside Rg3

Ginsenoside Rg3 originates from the plant genus *Panax*. It is a steroid glycoside and triterpene saponin that shows antioxidative, anti-inflammatory, and MMP activities. A clinical study demonstrated that ginsenoside Rg3 attained consistently high efficiency and few side effects when given with gestrinone. Ginsenoside Rg3 can be used as a clinical treatment for endometriosis [170]. Also, a previous study showed that the volume of endometriotic lesions reduced and the MVD was lower in ectopic tissues in the ginsenoside Rg3 usage group than in the gestrinone group. Additionally, ginsenoside Rg3 exerted an antiangiogenic effect by inhibiting the expression of the inhibitors of DNA binding 1 gene and neuropilin-1 gene in rat endometriosis models (Table **1**) [171, 172].

8.5. Resveratrol

Resveratrol is a polyphenol with anti-inflammatory effects. It is found naturally in berries, peanuts, and red wine. It exerts an anti-inflammatory effect by inhibiting the release of cytokines (TNF-α, IL-6, IL-8, VEGF, and MCP-1) and the production of reactive oxygen species in monocytes, macrophages, and lymphocytes (Table **1**). It inhibits the action of NF-kB that has a significant role in cell proliferation, apoptosis, and enlargement of neoplasms through regulating several cytokines and chemokines. Its mechanism of action and the pathophysiology of endometriosis may be similar, as indicated by a study that assessed its effect on an experimentally induced endometriosis rat model and found it to be ac-

tive against the progression of the illness through its antiangiogenic and anti-inflammatory properties [1].

Resveratrol has been suggested to treat endometriosis owing to its antioxidant properties. A previous study showed that resveratrol potentiated the effect of oral contraceptives in relieving endometriosis-related dysmenorrhea by inhibiting the expression of aromatase and COX-2 in the endometrium [173]. Likewise, resveratrol inhibited angiogenesis in peritoneal and mesenteric endometriotic lesions by decreasing MVD and proliferating activity of CD31-positive endothelial cells in the developing microvasculature of the lesions in rat endometriosis models treated with resveratrol for 4 weeks. However, at the same time, the growth of lesions was slow and their size was small in resveratrol-treated mice compared with controls owing to lower numbers of proliferating cell nuclear antigen- and Ki67-positive stromal and glandular cells [174].

Bruner-Tran *et al*. evaluated the effect of resveratrol on experimental endometriosis *in vivo* and the invasiveness of endometrial stromal cells *in vitro* [153]. They reported that resveratrol could decrease the progression of investigational endometriosis in a nude mouse model. They correlated these protecting effects of resveratrol to a decrease in endometrial cell proliferation and an increase in cell death. Nevertheless, the effects of resveratrol on the proliferation of endometriotic tissues were not clear; they found a reduction in MKI67 expression but an increase in proliferating cell nuclear antigen staining.

In a study by Bruner-Tran and Osteen (2010) [175], the ovariectomized nude mice were administered with a slow-release estrogen capsule 24 h prior to the intraperitoneal injection of normal proliferative human endometrial tissues. The use of resveratrol at the dose of 6 mg/kg was started 24 h after tissue injection and continued for up to 20 days. Scientists found that mice receiving resveratrol showed fewer lesions; however, the lesions in the controls were smaller and apoptotic. Prominently, resveratrol did not seem to influence apoptotic activity within the uteri of cured mice. Although the doses used were pharmacologic and could not be achieved from the normal ingestion of resveratrol-containing nutrients, the aforementioned findings might propose a possible role for resveratrol supplementation in treating endometriosis in women [176].

8.6. Baicalein

Jin *et al*. (2017) aimed to investigate the potential activities of baicalein on human endometrial stromal cells *in vitro*. Ectopic endometrium samples were gained from 6 female patients with endometriosis. In this study, immunocytochemistry was performed to verify the purity and homogeneity of the endometrial stromal cells, and in order to investigate cell viability, a Cell Counting Kit-8 assay was used. Cell cycle progression was conducted through flow cytometry. The effects of baicalein were evaluated on the expression of B-cell lymphoma 2 (Bcl-2), Bcl-2-associated X protein (Bax), proliferating cell nuclear antigen (PCNA) and cyclin D1 in endometrial stromal cells using western blot analysis. The results indicated that the application of baicalein significantly decreased the viability of human endometrial stromal cells by inhibiting the nuclear factor (NF)-κB signaling pathway (Table **1**). The application of baicalein significantly increased the number of cells in the G0/G1 phase, whereas the application of baicalein significantly reduced the number of cells in the S and G2/M phases. Jin *et al*. (2017) suggested that baicalein might suppress the viability of human endometrial stromal cells through the NF-κB signaling pathway *in vitro*. Thus, baicalein may provide a novel treatment option for endometriosis [177].

8.7. Palmitoylethanolamide (PEA)

PEA has anti-inflammatory and neuroprotective properties. Di Paola *et al*. (2016) reported that co-micronized palmitoylethanolamide/polydatin (PEA/PLD) decreased endometriotic lesions due to its antiangiogenic effect and also this combination decreased the levels of nerve growth factor, intercellular adhesion molecule, MMP-9, and lymphocyte accumulation (Table **1**) [116, 178].

8.8. Genistein

Genistein is a derivative of isoflavone. Isoflavones were shown to have anti-angiogenic activity in the previous studies [179]. The administration of genistein significantly decreased the expression of estrogen receptor α, VEGF and HIF-1α in peritoneal tissues, on the other hand increased the expression of estrogen receptor β in mice (Table **1**). Genistein also regulated angiogenesis by inhibiting upon the estrogen receptor in a murine model of peritoneal endometriosis [180].

8.9. Xanthohumol

Xanthohumol, prenylated flavonoid, was isolated from the female inflorescences of hops. Anti-proliferative, anti-inflammatory, and anti-angiogenic properties of xanthohumol were proven by previous studies. Xanthohumol was shown to effectively reduce the level of phosphoinositide 3-kinase protein in a BALB/c mouse model of endometriosis (Table **1**) and also xanthohumol significantly decreased the MVD. Thus, xanthohumol could be considered for the selective treatment of endometriotic lesions [181].

9. HERBAL FORMULATIONS USED FOR THE TREATMENT OF ENDOMETRIOSIS

Paeonia lactiflora Pall. “white peony” and *Rehmannia* sp. (Orobanchaceae) have remarkable anti-inflammatory and antispasmodic effects. They can be used to treat endometriosis, as suggested by Mills and Bone (2000) [182]. Studies using the latter showed that PGs in the myometrium were reduced through the inhibition of phospholipase A2. Also, arachidonic acid and platelet-activating factor were reduced, the free radical formation was inhibited, and smooth muscles were relaxed [183].

Glycyrrhiza glabra L. “licorice” root and *Calendula officinalis* L. “calendula blossoms” are used as anti-inflammatory agents and given as a formula to treat endometriosis [113]. Flowers of *C. officinalis* have vulnerary, antihemorrhagic, anti-inflammatory, and lymphatic properties, and may relieve the illness by supporting lymphatic drainage and reducing congestion. A recent study showed that standardized hydroalcoholic herbal therapies, such as *Calendula*, *Hypericum perforatum* L. “St. John’s wort” (Hypericaceae), *Plantago lanceo-*

Table 1. Plants/Compounds used for the management of endometriosis and their action mechanisms.

Plant/Compound	Action Mechanism	References
Andrographis paniculata	Decreasing the levels of COX-2 and tissue factor, the phosphorylation of p50 and p65	[116,117]
Viburnum opulus	Decreasing the levels of TNF-α, IL-6, VEGF	[118]
Angelica sinensis	Inhibiting PG synthesis Lessening inflammation	[121]
Achillea biebersteinii	Decreasing the levels of TNF-α, IL-6, VEGF	[125]
Echinacea sp.	Reducing inflammation	[126]
Tanacetum parthenium	Inhibiting PG synthesis, which stops arachidonic acid conversion into inflammatory PGs, mast cell degranulation, and subsequent release of histamine, serotonin, and other inflammatory cytokines	[127]
Lithospermum erythrorhizon	The regulation of activation normal T-cell expressed and secreted mRANTES levels in the peritoneal fluid	[129]
Hypericum perforatum	Estrogen binding properties when the estrogen levels are high in endometriosis	[130]
Vitex agnus-castus	Luteal phase dysfunction	[132, 133]
Vitex negundo	The anti-inflammatory and antioxidant activities	[135, 136]
Gossypium sp.	Antagonizing the effects of estrogen and progesterone	[137,138]
Paeonia lactiflora	Decreasing tissue-specific anti-endometrial immunoglobulin M antibody in patients with endometriosis	[139]
Alchemilla mollis	Decreasing the levels of TNF-α, IL-6, VEGF	[141]
Uncaria tomentosa	Inhibiting production of TNF-α, lipopolysaccharides, nitrites, and PGE2	[31]
Verbena hastata	Inhibiting human chronic gonadotropin, and immunomodulatory effects by inhibiting the phagocytosis of human granulocytes	[142]
EGCG	Suppressing the expression of VEGF-C and VEGF receptor 2 and reducing extracellular regulated kinase activation in endothelial cells	[154]
Curcumin	Reducing the number of microvessels and the protein expression of VEGF in the ectopic endometrium of rat endometriosis models	[160, 162]
Puerarin	Reducing the levels of MMP-9, ICAM-1, and VEGF protein	[169]
Ginsenoside Rg3	Antiangiogenic effect by inhibiting the expression of the inhibitors of DNA binding 1 gene and neuropilin-1 gene	[171, 172]
Resveratrol	Inhibiting the release of cytokines (TNF-α, IL-6, IL-8, VEGF, and MCP-1) and the production of reactive oxygen species in monocytes, macrophages, and lymphocytes	[1]
Baicalein	Inhibiting the NF-κB signaling pathway	[177]
Palmitoylethanolamide	Decreasing the levels of nerve growth factor, intercellular adhesion molecule, MMP-9, and lymphocyte accumulation	[178]
Genistein	Decreasing the expression of estrogen receptor α, VEGF and HIF-1α in peritoneal tissues	[180]
Xanthohumol	Reducing the level of phosphoinositide 3-kinase protein in a BALB/c mouse model of endometriosis	[181]

lata L. "plantain" (Plantaginaceae), and licorice, suppressed the effects of 5-lipoxygenase (5-LO) and COX-2, key enzymes in the formation of pro-inflammatory eicosanoids from arachidonic acid. It was suggested that licorice extract had remarkable anti-inflammatory properties and lacked the side effects usually encountered with COX-2 and 5-LO inhibitors. In addition, St. John's wort and plantain extracts may be classified as active herbal anti-inflammatory agents [32].

Sea buckthorn (*Hippophae rhamnoides* L.) and St. John's wort (*Hypericum perforatum* L.) traditionally have been used for the treating of uterus inflammation and endometriosis. A mixture of sea buckthorn and St. John's wort oils significantly decreased the volumes of endometriotic foci areas and reduced the levels of TNF-α, vascular VEGF and IL-6 in peritoneal fluids in rats [184].

CONCLUSION

Despite advances in technology, the achievements in terms of drug discovery are not many. Moreover, prominent differences have been observed in the structural and distributional characteristics of synthetic and natural molecules. In the present approach to remedy, the strategies are usually based on relieving the symptoms recognized or identified by patients. Conversely, this may frequently cause undesired pathologies. Nature provides an enormous source for discovering novel bioactive molecules owing to the irresistible structural and biological variability. Folk remedies are the most promising source for attaining this objective. Hundreds of active molecules in folk medicine have been identified using *in vivo* bioassay- or *in vitro* activity-guided fractionation and isolation techniques.

Endometriosis is a common health problem, which usually results in gynecological diseases. The present review revealed that treatment with medicinal plants and phytoconstituents of medicinal plants had a significant role in endometriosis. In recent years, the surge for the use of medical plants to treat endometriosis has increased. A number of plants have been used conventionally to control endometriosis and thus for treating many gynecological disorders. Additionally, various studies verified that constituents isolated from plants, for instance, epigallocatechin gallate, curcumin, puerarin, ginsenoside, and resveratrol, can be used to treat endometriosis. Hence, the use of medicinal plants and phytoconstituents of medicinal plants has been regarded as a novel approach for treating endometriosis and maintaining a healthy life. Additional long-term studies are required to support the safety of the constituents of medicinal plants, chiefly concerning the plant-drug interactions and the appropriate dosage. Comprehensive and planned studies, besides clinical assessment, derivatization, and formulation studies, may provide products benefiting human health.

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