

Review

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Phytotherapy in endometriosis: an up-to-date review

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Abstract:

Endometriosis is a benign gynecological disease which symptoms can provide a severe impact on patient's quality of life with subsequent impact on psychological well-being. Different therapeutic strategies are available to treat this disease, such as surgery, hormonal therapies, and nonsteroidal anti-inflammatory drugs. Nevertheless, the efficacy of conventional medical treatments is limited or intermittent in most of the patients due to the associated side effects. Therefore, a woman with endometriosis often search for additional and alternative options, and phytotherapy might be a promising alternative and complementary strategy. Different medicinal plants, multicomponent herbal preparations, and phytochemicals were investigated for pharmacological proprieties in endometriosis therapy. In most of the cases, the effect on endometriosis was related to phenolic compounds, such as flavonoids and phenolic acids reporting anti-inflammatory, proapoptotic, antioxidant, and immunomodulatory functions. Moreover, some phytochemicals have been related to a strong phytoestrogenic effect modulating the estrogen activity. Although promising, available evidence is based on in vitro and animal models of endometriosis with a limited number of well-performed clinical studies. There are almost none randomized control trials in this area. Therefore, properly constructed clinical trials are mandatory to achieve more conclusive results about the promising role of phytotherapy in the management of endometriosis.

Keywords: endometriosis, flavonoids, pharmacological treatments, phytochemicals, phytotherapy

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Endometriosis: An overview

Endometriosis is a benign gynecological disease that affects 5–10% of women in fertile age [1]. It is a chronic inflammatory estrogen-dependent pathology that consists in the presence of endometrial-like tissue, with stroma and glands, outside the uterus, involving peritoneum, adnexa, bowel, and other organs, in and outside the abdominal cavity, with superficial or deep infiltrating implants [2–4]. This ectopic endometrial-like tissue induces a chronic inflammatory response and damage–repair mechanisms with subsequent scar tissue formation and adhesions that are able to distort woman's pelvic anatomy [5–7]. Although it can be asymptomatic, in the majority of the cases it is related to dysmenorrhea, chronic pelvic pain, dyspareunia, abnormal uterine bleeding, and

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infertility [2, 8–10]. Symptoms, particularly pain, correlate poorly with the extension and grade of endometriosis, and the physiology of nociception and pain characteristics are not completely understood [10, 11]. Nevertheless, all these symptoms are able to provide a severe impact on patient's quality of life with a subsequent impact on psychological well-being [3, 12–17].

The full diagnosis of endometriosis requires surgical inspection, preferably with histological confirmation in collected specimen [18–20].

Furthermore, several studies have suggested an association between endometriosis and development of ovarian cancer with the predominant subtypes of epithelial ovarian cancer [21–24] while it is not fully understood if endometriosis may be also associated with endometrial and breast cancer [25–27].

Surgery represents a key treatment for the disease and aims to remove ectopic lesions and reestablish the normal anatomy, reporting reduced pelvic pain and improving reproductive outcomes [28–32]. Nevertheless, surgical treatment can be avoided when medical therapies achieve symptoms under control and counteract the disease development via pharmacological inhibition of ovulation and menstruation, although drugs do not cure the disease because lesions are not eradicated [33]. In these cases, medical therapy represents one of the most appropriate approaches based on the benefits versus the risks for the patients and the tolerability profile [34, 35]. This approach may allow avoiding repeated surgery for relapsing disease in young patients, allowing to plan the best moment to perform surgery during the reproductive age, if required [36]. Indeed, surgery is generally effective in pain relief, but its benefit is often temporary for the risk of relapsing disease, and due to this risk, medical therapies have a further key role in the management of patients in the postoperative period [11, 18, 37].

In the last few years, the advances in neuroendocrinology, endocrinology, tumorigenesis, neurogenesis, and genomics are transforming the current management approaches for endometriosis. In this regard, GnRH antagonists, SPRM/SERM, aromatase inhibitors, immunomodulators, and antiangiogenic drugs appear as emerging and promising medical treatments for endometriosis. Further studies are needed in order to promote personalized medicine for patients with endometriosis [38–40].

Pharmacological treatment for endometriosis

Usually, the medical therapy consists in different hormonal drugs, including combined hormonal contraceptives, progestogens, anti-progestogens, levonorgestrel-releasing intrauterine system, gonadotropin releasing hormone analogs with or without add-back therapies; and to date, there is no robust evidence to support a specific hormonal therapy over the others [3, 18]. Additionally, endometriosis requires the management of pain symptoms, and nonsteroidal anti-inflammatory drugs represent often the first line [41].

Although multiple pharmacological strategies are available, a recent systematic review showed that the efficacy of conventional medical treatments is limited or intermittent in most patients. Only in 29 out of 58 articles, involving 125 treatment arms, the response of pain symptoms to treatment was reported. About 5–59% of the women reported reduced or unchanged persistent pain, 11–19% of the women had experienced no reduction in pain at the end of the treatment, and 17–34% reported a recurrence of symptoms after treatment cessation [42]. Additionally, adverse effects and the impairment of the reproductive function of the pituitary–gonadal axis represent a cause of further concerns, that with the often-incomplete resolutions of symptoms are a cause of dissatisfaction with conventional treatments. About 5–16% of enrolled subjects discontinued the therapy due to adverse events or lack of efficacy [42–44]. On that basis, the woman with endometriosis often searches for additional and alternative options to improve their symptoms and psychological well-being like other gynecological diseases, such as fibroids [45]. A recent study reported that up to 76% of the total women affected by endometriosis use self-management strategies [46]. These complementary strategies include different options such as the application of heat, relaxation techniques and yoga, movement and stretching, rest, physiotherapy, psychotherapy, acupoint, diet changes and supplementations, and phytotherapy. These women reported that many of these natural treatments are effective in the management of endometriosis, although none of these strategies are entirely curative and neither can eradicate the endometriotic lesions, and the lack of safety and efficacy studies represent a limit to their uses [47–49]. Nevertheless, because conventional therapies are not completely effective in all women, individual treatment options should be discussed and initiated by clinicians to provide the best comprehensive treatment, and natural therapies represent a source of paramount importance that can contribute to the healing process and to the control of severe symptoms as they emphasize the general health and well-being [49].

Phytotherapy

Phytotherapy, with the use of medicinal plants, is a possible source of new strategies to manage the disease, as it was demonstrated in other gynecological disorders [48, 50, 51]. In this regard, literature about the topic confirms the positive effects of phytotherapy in the treatment of menopausal symptoms or sexual dysfunctions [52–54].

Different plants offer a variety of therapeutic properties and may be important sources of minerals, vitamin, and phytohormones.

Moreover, different pathways involved in the etiopathogenesis of endometriosis [55] can be a target of herbal medicines, supporting with molecular mechanism a possible effect [48, 56]. The decreased apoptosis and the improved cell survival are often reported in eutopic and ectopic endometrium of affected woman as compared to healthy controls, and some studies investigated the effect of different plants on apoptosis and cell survival [57–60]. Similarly, other pathways having a key role in the development of endometriosis were investigated as possible target of phytotherapy [56], such as angiogenesis mediated by vascular endothelial growth factor (VEGF) [49, 61], the altered inflammatory microenvironment involving cytokines and immune cells [62–64], the oxidative stress [65, 66], and the attachment and invasion mechanisms [67–69]. Moreover, there is evidence that specific herbs may have an impact on the epigenome, representing a therapeutic strategy to potentially reverse the aberrant epigenetic changes reported in endometriosis [70, 71]. On this basis, different plants were investigated as a complex group of molecular compounds effective in endometriosis [56].

Alchemilla

The genus *Alchemilla* (Rosaceae) including almost 100 species is used in phytotherapy to treat various gynecological and non-gynecological diseases, such as aphthous stomatitis [72]. These plants have a high content of phenolic compounds (flavonoids and tannins) that induce regeneration of skin epithelium and have anti-inflammatory and antiangiogenesis activities, that may explain the reported wound-healing proprieties and the reduced endometriosis formation in rat models [73–75].

Allium sativum

Allium sativum (garlic) has different pharmacological properties, such as the reduction of cardiovascular diseases risk, and the antitumor, antimicrobial, and antianxiety effects [76, 77]. It was associated with proapoptotic and anti-angiogenetic functions inducing caspase and downregulating VEGF [78, 79]. Some molecular derivatives of garlic were reported able to modulate inflammatory response suppressing leukocyte production of pro-inflammatory cytokines and improving the expression of interleukine-10 (IL-10). Moreover, they were reported able to reduce the oxidative stress improving antioxidant enzymes [80–83]. In endometriosis, it was reported able to reduce cell proliferation, attenuating the expression of VACM-1, ICAM-1, and other proteins involved in the migration and metastasis [76, 84].

Salvia miltiorrhiza

Salvia miltiorrhiza (danshen in Chinese) represents one of the most used plants in Chinese traditional medicine. Extracts from the root reported pharmacological activities such as antiviral, antioxidant, antimicrobial, anti-inflammatory, anticancer, and cardiovascular effects [85–87]. About anticancer effects, *S. miltiorrhiza* may prevent cancer initiation through antioxidation proprieties and may inhibit cells proliferation inducing apoptosis or autophagy [88]. *S. miltiorrhiza* extract reported antiproliferative, proapoptotic, and anti-angiogenetic functions, modulating caspases, proapoptotic proteins, and VEGF signaling [89–92]. Further studies reported the ability to modulate the expression of metalloproteases and adhesion molecules, such as ICAM-1 and VCAM-1, repressing invasion and growth of human cancer cells [93, 94]. These effects involve many pathways that may play a key role even in the endometriosis treatment. In endometriosis, extracts of this plant reduced the levels of cancer antigen 125 (CA-125) and of pro-inflammatory cytokines in the peritoneal fluids of rat models [95–97].

Artemisia princeps

Artemisia princeps (family Asteraceae) was associated with antitumor, antipyretic, antimalarial, antihemorrhagic, antioxidant, and antiviral properties. A decreased expression levels of ICAM-1 and VCAM-1 and a reduction of pro-inflammatory cytokines such as interferon- γ , IL-2, tumor necrosis factor- α (TNF- α), and IL-1 β were reported [98–100], consistently with the reduced cell proliferation of inflammatory T leukocytes [101]. Leaf extract has a proapoptotic effect on endometriotic epithelial cells suppressing expressions of antiapoptotic factors such as Bcl-2 and activating caspase in a dose-dependent manner [102].

Aloe vera

Aloe vera (genus *Aloe*, family Xanthorrhoeaceae) is a well-known topical and oral therapeutic agent for the beauty, medicinal, and skin care properties. This plant is used in phytotherapy for the gastrointestinal activities, the hepatoprotective properties, and the effects in skin problems, such as wounds, injuries, and infective diseases [103]. The mannose 6-phosphate present in Aloe gel is proposed as the active agent improving wound healing by increasing cell phagocytic activity, fibroblasts proliferation, and hyaluronic acid and collagen synthesis [104]. Moreover, *A. vera* was associated to a strong immunomodulatory activity with anti-inflammatory effects [105], to antioxidant properties [106] and to an anticancer activity modulating neo-angiogenesis, cell proliferation, and apoptosis [104]. On that basis, *A. vera* was tested in rat models of endometriosis, resulting in an inhibited formation and regression of endometriotic lesions and in a reduction of oxidative stress markers with a raise of antioxidant levels in the peritoneal fluid [107].

Viburnum opulus

The genus *Viburnum* (family Caprifoliaceae) comprises more than 230 species. Its fruits are widely used for the medical properties in different diseases, comprising heart disease, coughs, digestive troubles, and bleeding. Moreover, it was reported effective in gynecological disorders, such as primary and secondary dysmenorrhea and ovarian cysts [108]. In the endometriosis rat model, *Viburnum opulus* was reported associated with a reduction of endometriotic implants volume and to the remission of TNF- α , VEGF, and IL-6 levels [109].

Multicomponent herbal preparations

Different studies investigated multicomponent herbal preparations, demonstrating an efficacy via anti-inflammatory, antiproliferative, and proapoptotic mechanisms. First, a mixture of *Hippophae rhamnoides* L. and *Hypericum perforatum* L. oils demonstrated an anti-inflammatory and antiangiogenesis activities with an anti-endometriosis effect, reporting a significant volume reduction of endometriotic implants [48, 110]. Then, a mixture of *Curcuma zedoaria* and *S. miltiorrhiza* was applied in a clinical study to treat endometriosis compared with danazol. Study results were comparable, and the mixture was reported as effective and safe as medicine [111]. A rat model was used to test the Fubao Danggui Jiao that is a Chinese Materia Medica variant. The study reported a significantly reduced volume of the surviving endometriotic implants as compared with danazol [112]. Further different decoctions, traditionally used to treat endometriosis in China, were reported effective in the management of endometriosis, including Xuefu Zhuyu, Xiaochaihu, Qu Yi Kang, Yi Wei Ning, Yi Wei San, and Huoxue Xiaoyi [44]. Xuefu Zhuyu was reported effective in more than the 90% of cases in relieve dysmenorrhea similarly to mifepristone, and it was reported able to induce the shrink of ectopic lesions and promote fertility [48]. Xiaochaihu was reported able to reduce the expression of aromatase protein and COX-2 protein in endometriotic tissues [113]. Qu Yi Kang was related to the reduction of IL-2 and IL-6 levels in peritoneal fluid, to the inhibition of endometriotic tissue growth and proliferation, and to the reduction of estrogen receptor (ER) and VEGF protein expression within the endometriotic tissue in rat models [48].

There are numerous plants and multicomponent herbal preparations investigated for the medical management of endometriosis other than those reported, and a growing body of evidence, reporting promising results, suggests a potential key role of them in the treatment of endometriosis [56]. Nevertheless, although available evidence suggests a utility of phytotherapy in endometriosis and provides the molecular mechanism explaining the results, the majority of studies had been performed in cellular and animal models of endometriosis with a limited number of clinical studies. Therefore, it should be remembered that not enough data are available for the clinical recommendations of these plants and preparations, and further studies are required before their implementation in the management of endometriosis.

Specific phytochemicals

Behind the use of plants, some specific phytochemicals extracted from plants were investigated as a single agent with pharmacological proprieties in endometriosis, such as curcumin, genistein, and resveratrol.

Curcumin

Curcumin is the major chemical compound of *Curcuma longa* (Zingiberaceae) [114]. Research suggests that curcumin can help in the management of oxidative and inflammatory conditions, metabolic syndrome, arthritis, anxiety, and hyperlipidemia. Many pharmacological activities have been attributed to these compounds such as antioxidant, antiproliferative, anti-inflammatory, anticarcinogenic, and antibacterial activities [115, 116]. Curcumin was related to a reduction of estrogen level and stoma cells number in endometriotic implants [117]. It was reported able to induce apoptosis modulating pro- and antiapoptotic proteins, to inhibit angiogenesis via inhibition of VEGF signaling pathways, to modulate inflammatory response acting on the secretion of inflammatory mediators such as TNF- α and TGF- β 1, and to reduce oxidative stress. It also suppressed invasiveness via decreasing metalloproteases and modulating E-cadherin pathway [118–124]. These results suggest that it may help in the management of endometriosis as a dietary and pharmacological agent, but further research is necessary [125].

Genistein

Genistein is an isoflavone with strong phytoestrogenic effects, which is isolated from soy. A growing body of evidence, from in vitro and in vivo studies, reported a remarkable chemopreventive activity mediated by modulating the transduction of many genes involved in cell-cycle regulation, cell–cell and cell–matrix adhesion, invasion, apoptosis, and angiogenesis [126, 127].

This chemopreventive activity is consistent with the observed reduction of endometriotic implants dimension, that was explained by its antiproliferative and antiangiogenesis activity as well as the inhibition of enzymes involved in the steroid metabolism [128]. Genistein reported proapoptotic and anti-angiogenic functions explained by the modulation of different pathways involved in the apoptosis and downregulating VEGF [129, 130]. Additional studies demonstrate anti-inflammatory function and antioxidant activity, modulating cytokines and increasing antioxidant enzymes activities [131, 132]. Moreover, consistently with those reported in a study investigating the role of genistein as treatment and preventive agent in endometrial cancer, genistein inhibits cell proliferation through different pathways, including decreased ER expression and the subsequent alteration of the AKT/Mammalian Target of Rapamycin (AKT/mTOR) and Mitogen-Activated Protein Kinase (MAPK) pathways [133, 134]. This evidence may support a promising therapeutic and preventive effect of genistein even in endometriosis, although the role in endometriosis therapy requires additional research.

Resveratrol

Resveratrol is polyphenol produced by many plants and associated with antioxidant, anti-inflammatory, and anti-angiogenic functions [135]. It was reported able to reduce lipid peroxidation, to increase antioxidant capacity, to downregulate pro-inflammatory cytokines, to induce apoptosis and to promote cell differentiation in endometriosis rat models [136, 137]. The proapoptotic functions were related to the activation of mitochondrial pathway inducing autophagy [138]. Its anti-angiogenic effect was related to the inhibition of VEGF gene and the modulation of matrix protein gene expression. Resveratrol suppressed inflammation through NF- κ B and MAPKs signaling pathways, downregulating ICAM1 expression and upregulating KLF2 expression [138]. Moreover, it significantly counteracts oxidative stress enhancing the expression of different antioxidant enzymes and was reported suppressing invasion, migration, and proliferation of carcinoma cells [139–141]. On that basis, this phenolic compound could be considered a new innovative drug in the prevention and treatment of this disease, although further studies are needed. Indeed, available data are still conflicting [142]. A randomized clinical trial by Mendes da Silva et al. compared resveratrol (40 mg/day) with the monophasic contraceptive pill (Combined Oral Contraceptive (COC)) to COC with placebo for the reduction of pain scores in women with a laparoscopic diagnosis of endometriosis. Forty-four women were randomized to receive COC (levonorgestrel 0.15 mg/ethinyl estradiol 0.03 mg) for 42 days to be taken with identical capsules containing 40 mg of resveratrol or placebo. Pain symptoms were evaluated using a visual analog scale. According to the

results of this study, resveratrol is not superior to placebo for the treatment of pain in endometriosis [143]. Conversely, the studies by Maia et al. resveratrol potentiates the effect of oral contraceptives in the management of endometriosis-associated dysmenorrhea since it further decreases aromatase and cyclooxygenase-2 expression in the endometrium [144].

***Pinus pinaster* bark**

Pinus pinaster bark is commonly used as nutrition, supplemental food, and herbal remedy. It is rich in polyphenols, especially taxifolin and catechin [56]. Several studies have confirmed the effectiveness of this plant with particular reference to anti-inflammatory effects, decrease in serum thromboxane concentration, relief of menstrual disorders and pregnancy-associated pain, and endometriosis, antimicrobial, and antiviral activities [145, 146].

It has been demonstrated that *P. pinaster* bark reduces symptoms without influencing menstrual cycles and estrogen levels in patients with endometriosis. Furthermore, it induces caspase-independent apoptosis [56].

Prunella vulgaris

Extracts of *Prunella vulgaris* (*Lamiaceae*) are currently used against HIV, herpes simplex virus, and allergic reactions, thanks to its antioxidative, antimicrobial and antiviral effects [56].

P. vulgaris is particularly rich in triterpenoids, flavonoids, tannins, oleanolic acid, betulinic acid, ursolic acid, polysaccharide prunelline, and rosmarinic acid [147].

P. vulgaris extract blocks the proliferation of ectopic endometrium and shows significant antiestrogenic properties [148]. Furthermore, it shows proapoptotic activity and decreases vascular inflammation through the suppression of the p38 ERK/MAPK signaling pathway and the inhibition of TNF- α -induced expression of intercellular adhesion molecules [149].

Inositol

The term inositol is commonly used to refer to a group of cyclic organic compounds belonging to the sugar family (molecular formula $C_6H_{12}O_6$) [150].

It is naturally found in cereals, corn, beans, and meat and is involved in several biological processes, among which endocrine function and reproduction [150, 151].

Myoinositol and D-chiroinositol (DCI) are the most known stereoisomers of inositol and the widest distributed in the human organism [150]. In recent years, several studies have investigated inositols as insulin-sensitizing integrative agents acting to, directly and indirectly, influence ovarian function. In this regard, it has been extensively reported that inositols have a key role in the treatment of infertility related to polycystic ovary syndrome, one of the commonest endocrine disorder among women of reproductive age [152–154].

Recently, the possible use of inositol (in particular, DCI) is also discussed to improve the fertility of patients suffering from endometriosis, thanks to its properties of oxidative stress reduction. Further studies are needed in order to better evaluate the potential efficacy and safety of DCI supplementation in balancing the oxidative status of patients suffering from endometriosis [155].

Conclusion

Based on the partial success of available interventions for the treatment of endometriosis, discovering new pharmaceutical agents seems to be necessary [3]. Phytotherapy, including medicinal plants, phytochemicals, and multicomponent herbal preparations, reported promising results from in vitro animal and human studies. In most of the medicinal plants, the effect on endometriosis can be attributed to phenolic compounds such as flavonoids and phenolic acids and their plant-derived secondary metabolites. These molecules reported the different mechanism of action including anti-inflammatory, antiproliferative, proapoptotic, antioxidant, antiangiogenesis, and immunomodulatory functions. Moreover, some investigated that phytochemical has been related to a strong phytoestrogenic effect modulating the estrogen activity.

Although available evidence suggests a utility of phytotherapy in endometriosis and provides the molecular mechanism explaining the results, the majority of studies had been performed in cellular and animal models

of endometriosis with a limited number of clinical studies [46, 50]. Therefore, the amount and quality of the available data are still insufficient to support a wide clinical application of phytotherapy for the management of endometriosis, and well-conducted clinical trials are mandatory to achieve more conclusive results about the role of phytotherapy in the management of endometriosis. However, because the treatment should be individually tailored to fit patients' needs, and a shared decision-making approach between patient and physician is greatly encouraged, available data may be enough to support phytotherapy as a potential and interesting addition to standard therapy schemes to provide a better control of endometriosis.

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