Novel herbs and drugs for endometriosis management: A review on current and futuristic therapies

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ABSTRACT

A disorder with estrogen dependency comprising of inflammatory lesions outside the uterus, causing pain and inflammation in pelvis and affecting women of reproductive age with infertility and post reproductive age is endometriosis. Endometriosis is viewed as public health issue with a major impact on quality of life of women. Medically advanced computational and chemical treatments are available to treat the progression of the disease by diagnostic imaging, clinical examinations, imaging and laparoscopy often leading to immediate surgery. A warrantable rethinking on the diagnosis and management of endometriosis is to be assessed and medical treatments should be considered as first-line option for therapeutic relief for endometriosis by suppressing the systemic estrogen levels providing desirable efficacy and safety, prior to performing endometriosis surgery. The aim of this review is to describe natural products, hormonal and non-hormonal compounds that suppress the progression of endometriosis. Various herbal, conventional and traditional therapies are investigated to treat gynecological disease, endometriosis. The information in this paper include various studies assessing the use of novel treatments in addition to the herbal and hormonal products in the endometriosis therapy. Most of the studies involved were in scrutinizing the pharmacological activity profiles of various sources of drugs in endometriosis treatment, hormonal drugs involved suppression and regulation of various hormones along with various factors like anti-inflammatory, anti-oxidant, anti-proliferative and apoptotic, anti-angiogenic, anti-invasive, immunomodulatory, and estrogen modulating activity. However, novel drugs and medicinal plants are also reviewed here to draw attention to the molecules of drugs that target at multiple points for rational therapeutic treatment of endometriosis.

INTRODUCTION

Endometriosis is a gynecological benign chronic inflammatory disorder that is described with the distinctive feature of dislodging of the endometriallike gland and stoma cells lining the uterus to outside the uterine cavity. It occurs more commonly in the pelvis and has an effect on a woman’s reproductive organs contributing to infertility and dysmenorrhea (Guo, 2015; Edwards et al., 2013). It mainly affects women in reproductive years and may also
of endometriotic cells, invasion, and neoangiogenesis. The shedding of endometrial tissue in the ectopic region leads to overproduction of mediators involved in inflammation like cytokines and prostaglandins causing chronic inflammatory reactions in the cells thereby resulting in adherence and scars, mediating pain and later infertility thereby affecting the quality of life (QoL) of woman. The symptoms of the disease depend on the location of endometriosis: intestinal symptoms can occur in case of bowel endometriosis, urinary symptoms in case of bladder or ureteral endometriosis. The etiology of endometriosis is found to be a complex intervention of genetic, anatomic, immunologic, and environmental factors which has a major effect on women’s vulnerability in the development of this disease.

Numerous medical therapies for treating endometriosis include the possibility to opt for the most acceptable treatment, based on pain intensity, age, fertility, route of administration, costs and QoL. Developing novel targets to treat this disease is the target of medical science as the growth, prolongation and development of endometriosis depend on mechanisms like proliferation of cells, immunity, apoptosis, and angiogenesis (Vercellini et al., 2014).

Endometriosis-associated pain is treated successfully by suppressing the production of estrogen and amenorrheal induction thereby creating low estrogen content depressing the growth, development and progression of endometrial tissues in the ectopic region. Current medical therapy involves interpretation of the process of the disease to alleviate the disease symptoms and may require surgical and medical intervention.

The aim of this review is to consolidate the recent advancements in the hormonal, biological and herbal drugs to relieve from endometriosis.

**Classification of Endometriosis**

Endometriosis can be classified into 5 types and have been tabulated in Table 1.

**Theories of Endometriosis**

Various theories on endometriosis have been discussed in Table 2.

**Diagnosis for Endometriosis**

The various diagnostic methods for endometriosis are tabulated in Figure 1.

1. Magnetic Resonance Imaging
2. Clinical Examination
3. Transvaginal Sonography
4. Transvaginal Ultrasonography

**Therapies**

All the currently available treatments are suppressive rather than being curative and the symptoms reoccur after cessation of treatment (Rivera et al., 1999). Present therapies for endometriosis target in treating the symptoms and lower the recurrence of disease by suppression of estrogen levels locally or systemically and its effects on lesions of endometriosis or targeting the lesions of endometriosis.

**Hormonal Therapies**

**Hormonal action of progestins and oestrogen-progestin combinations**

An effective way of treating endometriosis during the period in which the disease occurs which is reproductive age is by contraception to avoid pregnancies thereby treating the disease. The primary mechanism of the contraceptive action of combined hormonal contraceptives (CHCs) is considered to be the prevention of ovulation and not allowing the production of progesterone. They are considered to be the first line medical therapies for endometriosis. According to Vercellini et al. study, the beneficial effects of hormonal drugs which causes suppression of ovulation and menstruation and pain which was found effective in estrogen-progestins and progestins. The ability to induce atrophy of eutopic and ectopic endometrium, possessing anti-inflammatory and proapoptotic properties by these compounds by various novel routes was exclusively studied and proved (Vercellini et al., 2016).

Harada et al. investigated the effectiveness and safety of Ethinylestradiol/ drospirenone for management of endometriosis and it was found to have shown an increased efficacy significantly when compared to placebo in endometriosis patients (Harada et al., 2017). Studies also have indicated that women with problems related to menstrual cycle may move from continuous administration to use of a combinational therapy during cyclic phase.

Vercellini et al. investigated the comparative treatment of hormonal combination (desogestrel-ladetnyloestradiol) and goserelin depot and observed that deep dyspareunia was significantly decreased in both groups, with goserelin proved to be a superior treatment when compared to the combinational therapy of hormonal drugs (Vercellini et al., 1993).
Table 1: Classification of endometriosis

| Types                          | Location                                      |
|-------------------------------|-----------------------------------------------|
| Deep endometriosis            | Vesicouterine fold                            |
| Deeply infiltrating endometriosis | Peritoneal surface                          |
| Stromal endometriosis         | Stromal cells                                 |
| Ovarian endometriosis         | Endometrial tissue in the ovary               |
| Pelvic endometriosis          | Superficial peritoneal implants, Endometriomas |
| Deep pelvic endometriosis     |                                               |

Table 2: Pathogenesis of endometriosis

| Theories on endometriosis | Definition                                                                                   |
|---------------------------|----------------------------------------------------------------------------------------------|
| Retrograde Menstruation   | Sloughing of eutopic endometrium during menstruation via fallopian tubes into the peritoneal cavity |
| Bone Marrow               | Mesenchymal Hematopoietic stem cells are the endothelial precursors of endometriosis.        |
| Coelomic Metaplasia Theory| The visceral and abdominal peritoneum cells undergo metaplasia and form endometriosis.       |

Figure 1: Diagnosis for Endometriosis

Combined Oral Contraceptives (COCs)

Combined Oral Contraceptives (COCs) is medical treatments given as first line for endometriosis. The mechanism of action of COCs is the inhibition of GnRH, FSH and the LH surge in the mid cycle by estrogen and progestin.

Gonadotropin-Releasing Hormone Agonist

GnRH-agonist (goserelin, leuprolide, nafarelin, buserelin, triptorelin) decapeptides prove to be the second line therapies with their ability to decrease levels of LH and FSH by suppression of the production of ovarian estrogen by down regulation of GnRH receptors at pituitary level.

Gonadotropin-Releasing Hormone Antagonists

The usage of GnRH antagonists has been widely applied due to their suppression in the production of LH and FSH. Oral GnRH antagonists suppress gonadotropin production and produce a dose

Non-Steroidal Anti-inflammatory Drugs (NSAIDs)

NSAIDs is used in chronic inflammatory conditions, effectively relieving primary dysmenorrhea, hence proving to be the first line of treatment.
dependent environment of low estrogen levels. This causes the inhibition of proliferation and invasion of endometriotic cell thus maintaining the levels of estradiol sufficiently in circulation. Laboratory work resulted in proving GnRH-antagonists effects on endometriosis.

Selective Estrogen Receptor Modulators

The non-steroid ligands of Estrogen Receptors are Selective Estrogen Receptor Modulators (SERMs) possessing tissue-specific agonist, antagonist, or mixed agonist/antagonist activity. Raloxifene, a SERM used in postmenopausal osteoporosis and estrogen-responsive breast cancer (FDA approved). The SERM Bazedoxifene (BZA), antagonizes the endometrial stimulation induced by estrogen.

Selective Progesterone Receptor Modulators

Selective Progesterone Receptor Modulators (SPRMs) are ligands of Progesterone Receptors. Examples of SPRMs include Mifepristone (RU 486), Asoprisnil and Ulipristal acetate. Mifepristone (RU 486) proved to have antiproliferative effects in vitro endometrial stromal cells.

Non Hormonal Therapies

Cyclooxygenase-2 inhibitor

1. Rofecoxib
2. Celecoxib

Acupuncture

1. Relief of pelvic pain
2. Treatment of infertility
3. Treating dysmenorrhea

Antiangiogenic agents

1. Romidepsin
2. Parecoxib.

Herbal Remedies

The causative agent in progression of endometriosis in body is estrogen that needs to be deprived. Hence food supplements that reduce the levels of estrogen can be a supplemental therapy to deal with the disease. To deal with this progressive physical and metabolic alteration in an extraordinary way is to modify the diet that may help to alleviate the effects of disease. Certain foods create chemical reactions in the body and thereby have a promoting effect on endometriosis. A balanced and proper diet can help balance the estrogen levels. Another causative agent that was found to have both positive and negative effects on endometriosis was found to be prostaglandins. Medicinal plants and their active compounds have significant, antioxidant, anti-inflammatory, analgesic and proliferative properties which may help to treat the disease.

Management of endometriosis involve herbal medicines that target have pharmacological effects.

Medicinal plants for treatment against endometriosis

Investigational medicinal plants and phytochemicals for endometriosis treatment are listed below.

*Achillea biebersteinii* (Yarrow) from family Asteraceae

Demirel et al. investigated the role of various extracts of the aerial parts of *Achillea biebersteinii* in treatment of endometriosis and tested its effect on animal endometriosis model and proved that after treatment, volumes of endometrial foci, TNF-α, VEGF, and IL-6 were reduced in the ethyl acetate extract-treated group and no adhesion was detected in extract treated group. A promising alternative for treating endometriosis is ethyl acetate extract of *A. biebersteinii* due to the flavonoid aglycones found in the extract (Demirel et al., 2014).

*Andrographis paniculata* from family Acanthaceae

Zheng et al. isolated andrographolide, labdane diterpenoid from the plant aerial parts and proved that the plant has tumor depressing activity and inhibition of angiogenesis of tumor and endometriotic lesion volume reduction activity which is a promising alternative for treating endometriosis (Zheng et al., 2018).

*Angelica sinensis* from family Apiaceae

Wang et al. used the fluid extract of the plant and used it to treat dysmenorrhea and severe bleeding. The extract was administered 7 days prior to menstruation and it inhibited PG synthesis and lessened the inflammation thereby reducing menstrual pain and chronic endometritis. Blood circulation was stimulated by inhibiting the in vitro synthesis of thromboxane A2 (Wang et al., 1993).

*Alchemilla vulgaris* from family Rosaceae

Stanilova et al. experimented on actions of inflammatory inhibition on the species and proved that the actions were because of high concentration of phenol. The effects of two Alchemilla species- *Alchemilla lamollis* (Buser) Rothm. and *Alchemilla persica* Rothm. on experimentally induced endometriosis in rat and showed significant inhibition of for-
mation of cyst and endometrioma thereby proving the inhibitory activity on oxidation, inflammation and angiogenesis. Their phenolic constituents such as hyperoside and isoquercetin showed beneficial effects (Stanilova et al., 2012).

**Allium sativum** from family Liliaceae

Kim et al. showed cell proliferation reduction in TNF-α-activated human endometrial stromal cells by hexane extract of aged black garlic (Kim et al., 2013b).

**Artemisia princeps** from family Asteraceae

Kim et al. investigated and proved that leaf extract produced apoptosis by modulation of NF-kB and p38 pathway (Kim et al., 2013a).

**Coccinia cordifolia** from Family Cucurbitaceae

Jha et al. proved that *C. cordifolia* fertility induction in experimentally induced endometriosis female rats was not possible but the weight of endometrial implants reduced due to inhibitory effect on endometrial cell proliferation (Jha et al., 2010).

**Centella asiatica** from Family Apioideae

*Centella asiatica* has an effect on inflammation and microbial reduction. Ivanov et al. proved that centella asiatica in combination with other herbs can treat endometriosis or to help in recovery after the surgery (Ivanov et al., 2008).

**Copaifera langsdorffii** trees (Leguminosae- Caesalpinoideae family)

Nogueira Neto et al. proved the effect of inflammatory, nociceptive, microbial, cytotoxic, tumor reduction activity, and ulcer healing activity of *C. langsdorffii* oil in endometrial growth in rats with endometriosis (Neto et al., 2011b).

**Curcuma longa** from Family Zingiberaceae

According to Chen et al. and Zhang et al. Curcumin, a major polyphenolic chemical found in "Turmeric" *Curcuma longa* (Zingiberaceae) stimulates antioxidant, anti-inflammatory, and antiproliferative, endometriosis symptomatic relief and microcirculation (Chen et al., 2010).

Zhang et al. suggested 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.

Zhang et al. reported that curcumin decreased the number of endometriotic stromal cells (Qinshu et al., 2012).

**Echinacea sp.** From family Asteraceae

Sharma et al. investigated *Echinacea sp.* and proved the antioxidant use of the species by stimulating the immune system, increase in phagocytes, cytokines, and immunoglobulins production and anti-inflammatory action (Sharma et al., 2009).

**Euterpe oleracea** from family Arecaceae

Machado et al. investigated *E. oleracea* extract and proved that the extract exhibited anti-angiogenic and anti-inflammatory effects and decreased implant size (Machado et al., 2016).

**Gossypium sp.** from family Malvaceae

Bensky et al. has proved that the active ingredient, gossypol, has been found to have antagonistic effects of estrogen and progesterone (Bensky et al., 2004).

**Lithospermum erythrorhizon** from family Boraginaceae

Hisa et al. investigated shikonin has wound healing, antimicrobial, anti-inflammatory, antitumor, and antioxidant activities. It has been considered to have inhibitory effect on angiogenesis (Hisa et al., 1998).

**Paeonia lactiflora** from family Paeoniaceae

Tanaka et al. proved that *Paeonia lactiflora* can treat endometriosis due to the presence of abnormal monoterpene paeoniflorin that has cage structure in the peeled root of the plant and also displayed antispasmodic effects in ileum and uterus smooth muscle when given oral decoction to laboratory animals. A Paeonia formula from Eastern tradition decreased the antiendometrial immunoglobulin M antibody levels in patients. Paeonia may also balance the estrogen-progesterone to normal levels (Tanaka et al., 2000).

**Pinus pinaster** from family Pinaceae

According to Kohama et al., the compound Pycnogenol had no influence on menstrual cycles and levels of estrogen in patients with endometriosis but symptom scores were reduced (Kohama et al., 2007).

**Prunella vulgaris** from family Lamiaceae

Flavonoids, ursolic acid, Triterpenoids, polysaccharide prunelline, tannins, oleanolic acid, betulinic acid, and rosmarinic acid are the major chemical constituents of *Prunella vulgaris*. Collins et al. isolated the extract and experimented on blocking the proliferation of ectopic endometrium and demonstrated that the antiestrogenic properties were significant (Collins et al., 2009).

**Salvia miltiorrhiza** from family Lamiaceae

According to Zhou et al., the extract markedly decreased Cancer antigen 125 (CA-125) serum levels of estrogen in patients with endometriosis.
level and pro-inflammatory cytokines level in the endometriotic rat peritoneal fluid. The levels of IL-13 in the peritoneal fluids were also increased due to anti-apoptotic tanshinone IIA (Zhou et al., 2012).

**Tripterygium wilfordii** from family Celastraceae

Xiao et al. investigated that on administration the volume of endometrial implants and serum FSH and LH levels decreased and anti-endometrial antibody level normalized (Xiao et al., 2002).

**Uncaria tomentosa** from family Rubiaceae

Rojas-Duran et al. isolated Mitraphylline from bark of the plant and concluded the inhibition of IL-1α, 1β, 17, and TNF-α caused anti-inflammatory activity (Rojas-Duran et al., 2012).

**Viburnum opulus** from family Caprifoliaceae

In a study by Wichtl et al. demonstrated the stimulated secretion of FSH and LH when hot water extracts of European Verbena were administered. Fruits of *V. opulus* contains chlorogenic acid which reduced endometriotic volumes and inflammatory and angiogenic levels in endometriosis in rats (Wichtl, 2004).

**Vitex negundo** from family Verbenaceae

Amuthan et al. reported the reduction in size of endometrial cyst and endometrial epithelial morphology rupture (Amuthan et al., 2016).

**Zingiber officinale** from family Zingiberaceae

**Curcumin**

Curcumin is a compound polyphenol from Curcuma longa rhizomes. Haghi et al. studied the antioxidant, anti-inflammatory, and has actions against proliferation, carcinogen, and bacteria (Haghi et al., 2017).

**Epigallocatechin-3-gallate**

Epigallocatechin Gallate (EGCG) is a catechin, a major flavonoid of Camellia sinensis, common monomer from green tea. Xu et al. studied that EGCG inhibited microvessels in endometriotic implants and inhibited angiogenesis both in vitro and in vivo (Xu et al., 2011).

**Genistein**

Genistein is isolated from soy which is an isoflavone, a strong phytoestrogenic. Lin et al. experimented on Genistein, a derivative of isoflavone showing anti-angiogenic activity. The administration of genistein significantly decreased the expression of estrogen receptor α, VEGF and HIF-1α in peritoneal tissues and the expression of estrogen receptor β in mice was increased (Lin et al., 2014).

**Ginsenoside**

Ginsenoside Rg3 is from Panax. It is a glycoside that is steroidal in nature and triterpene saponin that has antioxidant and anti-inflammation action. Long et al. concluded that this plant can be used for endometriosis (Long and Li, 2012).

**Palmitoylethanolamide (PEA)**

PEA has actions against inflammation and positive effects of neuroprotectivity. Di Paola et al. reported that palmitoylethanolamide/polydatin (PEA/PLD), when co-micronized, decreased endometriotic lesions due to its actions against angiogenesis and decreased the nerve growth factor levels, intercellular adhesion molecule, MMP-9, and lymphocyte accumulation (Paola et al., 2016).

**Parthenolide**

A naturally occurring sesquiterpene lactone from Tanacetum parthenium. (L.) Sch. Bip. Takai et al. studied the role of parthenolide in diminishing TNF-α--induced IL-8 gene and expression of protein and TNF-α--induced COX-2 expression and PGE2 synthesis in human endometriotic cells (Takai et al., 2013).

**Puerarin**

An isoflavonoid obtained from Radix puerariae. According to Cheng et al., its weak estrogenic property is contributed by its binding to estrogen receptors (Cheng et al., 2012).

**Resveratrol**

A polyphenol with actions against inflammations by the release of cytokines and the production of...
Table 3: Novel herbal therapies of endometriosis

| Herbals                                      | Research study                                               | Conclusion                                                       | References                      |
|----------------------------------------------|--------------------------------------------------------------|------------------------------------------------------------------|---------------------------------|
| Danggui shaoyao powder (DSP)                 | Danggui shaoyao powder (DSP) for endometriosis treatment     | Effective but unclear molecular mechanisms                       | (Zhang et al., 2019)            |
| Gyejibokryeonghwan (GBH) and Bogol-gongjin-dan (BGD) | Treatment of a patient with endometrioma                     | The combination therapy of proved effective in treatment for endometrioma | (Park, 2019)                    |
| Rosmarinus officinalis leaves and Scutellaria baikalensis root | Effect of carnosic acid, rosmarinic acid and wogonin in vitro and in vivo | The rosemary (Rosmarinus officinalis) leaves, a Chinese herbal medicine used for endometriosis treatment in relieving symptoms and improving fertility. Wagnonis has effects on endometriosis inhibition is a flavonoid isolated from the root of the medicinal herb Huang Qin (Scutellaria baikalensis), | (Ferella et al., 2018)          |
| Traditional Korean Medicine (TKM)            | Inhibitory effect on the recurrent endometriosis after laparoscopic excision and hormone therapy | Positive effect on inhibition of recurrent endometriosis after laparoscopic excision and hormone therapy | (Kim and Yoo, 2018)             |
| Chinese Herbal Medicine (CHM)                | Safety, efficacy, consistency and target actions of CHM      | Fertility improvement                                             | (Jiang et al., 2017)            |
| Viburnum opulus L                            | Treatment of a patient with endometrioma                     | Chlorogenic acid, fruit extract of Viburnum opulus has positive effect on inhibition of endometriosis | (Saltan et al., 2016)           |
| Cat’s Claw (Uncaria tomentosa)               | Macroscopic and histological changes after the drug treatment | Positive effect on inhibition of endometriosis                   | (Neto et al., 2011a)            |

reactive oxygen species in monocytes, macrophages, and lymphocytes. Its antioxidant properties are suggestive to treatment of endometriosis. Maia et al. showed that resveratrol shows potentiating effect in endometriosis-related dysmenorrhea when used in combination with oral contraceptives inhibited aromatase expression and COX-2 in the endometrium (Jr et al., 2012).

**Xanthohumol**

Isolation from the female inflorescences of hops, a prenylated flavonoid was found to exhibit anti-proliferative, anti-inflammatory, and anti-angiogenic properties. Xanthohumol was shown to effectively reduce phosphoinositide 3 kinase protein level (Rudzitis-Auth et al., 2012).

**Home Remedies for Endometriosis**

Heat is found to have soothing effect on abdominal muscles by causing relaxation of the muscles in the uterus. The food habits to be practiced to avoid or to get relief from dysmenorrheal are avoiding refined carbohydrates, Eliminating sugary foods and processed sugar, Eliminating dairy and reducing red meat and egg yolk consumption to at most 2-3times a week. No scientific studies support the theory of essential oils increasing blood circulation, reduce spasms and consequently lead to pain reduc-
tion. Other approaches, such as yoga or body therapies, may reduce pelvic pain by improving flexibility of spine and pelvis strengthening.

**Novel Herbal Therapies**

An estrogen-dependent disease with extra uterine inflammatory lesions, causing infertility and dysmenorrhea. The primary target of conventional therapies is to reduce systemic levels of estrogens but do not produce effective actions and produce side effects. Therefore, the interest in the Herbal medicine is growing. The various novel herbal therapies are tabulated in Table 3.

**Novel Treatments**

**Elagolix**

Elagolix is used for treatment for pain related to endometriosis, orally. This drug suppresses levels of estrogen and progesterone hormones through antagonistic effects on GnRH receptor. This helps in inflammatory reduction and the endometrial tissue proliferation (Fantasia, 2019).

**Anastrazole**

Anastrazole is currently used to treat hormone receptor-positive breast cancer in post-menopausal women (Amsterdam et al., 2005).

**Shock Wave Therapy**

When medication is not satisfactory, or not tolerated or surgery is unwanted, a less invasive treatment, a novel approach to endometriosis treatment (Melki, 2019).

**Statins**

L.Gibra et al. studied the systemic review to understand the statins mechanism apoptosis stimulation, endometrial cell proliferation inhibition, angiogenesis blockade, adherence and invasion by endometrial cells interference into the peritoneum and oxidative stress and inflammation decrease (Gibran et al., 2014).

**Nicotinic Acetylcholine Receptor**

The anti-inflammatory and anti-nociceptive functions of nicotinic acetyl choline receptors (nAChRs) are of current researcher’s interest as nicotinic acetylcholine receptors may be a novel therapeutic target for Endometriosis (Wu et al., 2011).

**CONCLUSION**

Elimination of pain and/or infertility is the current medical and surgical treatment option for suppression of lesion proliferation. Further care and treatment should shift toward a centering patient rather than single symptom, approaching in multidisciplinary level. The biology of endometriosis and possible endometriosis subtypes has to be ventured deeply that may lead to novel therapeutic outcomes and broader plans in personalized treatment. Broader research on gene targeted and its associated treatments may provide relief from endometriosis. Development of analogue molecules of herbs can be of futuristic research. The present need is to alleviate pelvic associated pain and infertility by exploration of quality clinical trials or establishment of simplified special registration procedures for specific molecules of herbs with safe traditional use.

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**Conflict of Interest**

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