



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

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Article History:

Received on: 04 Mar 2021

Revised on: 05 Apr 2021

Accepted on: 07 Apr 2021

Keywords:

Endometriosis,
Fertility,
Future Medical Therapy,
Hormonal Drugs,
Herbs

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.

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ISSN: 0975-7538

DOI: <https://doi.org/10.26452/ijrps.v12i2.4699>

Production and Hosted by

IJRPS | www.ijrps.com

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INTRODUCTION

Endometriosis is a gynecological benign chronic inflammatory disorder that is described with the distinctive feature of dislodging of the endometrial-like 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 affect menopausal women. The factors leading to the growth, development and relapse of the disease are proliferation 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 antiinflammatory 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 combination therapy during cyclic phase.

Vercellini *et al.* investigated the comparative treatment of hormonal combination (desogestrel/ ethinylestradiol) 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 combination therapy of hormonal drugs (Vercellini *et al.*, 1993).

Combined Oral Contraceptives (COCs)

Combined Oral Contraceptives (COCs) is medical treatments given as first line for endometriosis. The

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

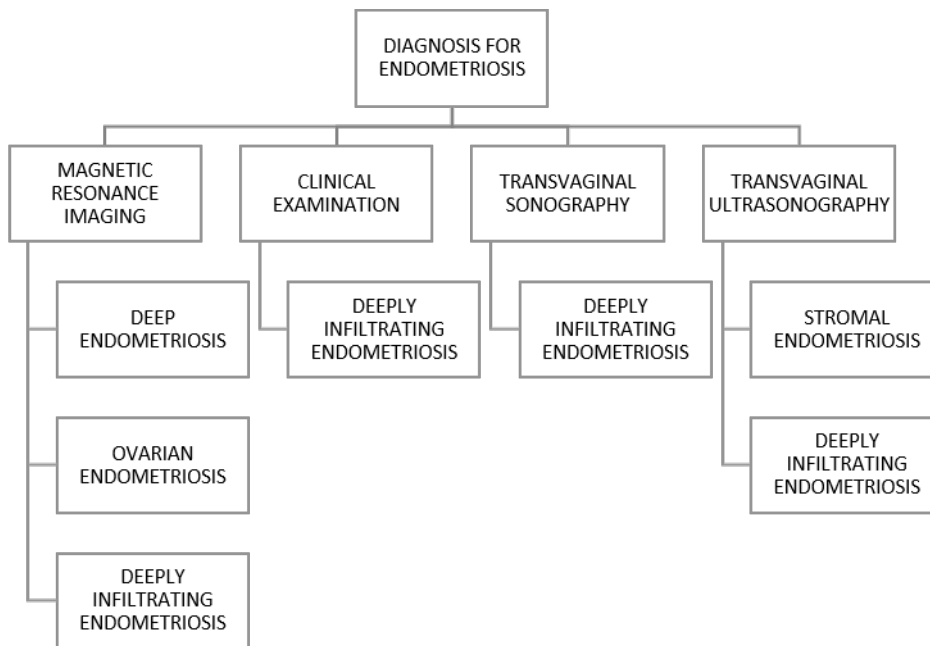


Figure 1: Diagnosis for Endometriosis

mechanism of action of COCs is the inhibition of GnRH, FSH and the LH surge in the mid cycle by estrogen and progesterin.

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.

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 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 of 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 mollis* (Buser) Rothm. and *Alchemilla persica* Rothm. on experimentally induced endometriosis in rat and showed significant inhibition of formation 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 Apiaceae

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 symptom 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 immunoglobins 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, antiinflammatory, 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

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-1 α , 1 β , 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**

Zingiber Officinale "ginger" root is used as symptomatic relief from inflammation and spasm caused due to dysmenorrhea affected by endometriosis.

Plant Chemicals Used in Endometriosis Treatment

Apigenin- a flavonoid

According to Park *et al.*, the flavonoid phyto-constituent has inhibitory effect on proliferation, inflammation and angiogenic properties (Park *et al.*, 2018).

β - caryophyllene- a natural sesquiterpene

Abbas *et al.* aim to investigate the suppressive potential of β -caryophyllene on endometriotic implant growth (Abbas *et al.*, 2013).

Baicalein

Jin *et al.* investigated the significant baicalein activities on human endometrial stromal cells from 6 female patients in vitro.

The usage of baicalein decreased human endometrial stromal cells viable count by inhibiting the nuclear factor (NF)- κ B signaling pathway (Jin *et al.*, 2017).

Curcumin

Curcumin is a compound polyphenol from *Curcuma longa* rhizomes. Haghi *et al.* studied the antioxidant, antiinflammatory, 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-1" 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 <i>et al.</i> , 2019)
Gyejibokryeonghwan (GBH) and Bogolgongjin-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 baicalensis 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. Wagoninis has effects on endometriosis inhibition is a flavonoid isolated from the root of the medicinal herb Huang Qin (Scutellaria baicalensis),	(Ferella <i>et al.</i> , 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 <i>et al.</i> , 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 <i>et al.</i> , 2016)
Cat's Claw (Uncaria tomentosa)	Macroscopic and histological changes after the drug treatment	Positive effect on inhibition of endometriosis	(Neto <i>et al.</i> , 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, antiinflammatory, and anti-angiogenic properties. Xanthohumol was shown to effec-

tively 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).

Anastrozole

Anastrozole 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.

Funding Support

The authors declare that they have no funding support for this study.

Conflict of Interest

The authors declare that there is no conflict of interest for this study.

REFERENCES

- Abbas, M. A., Taha, M. O., Zihlif, M. A., Disi, A. M. 2013. β -Caryophyllene causes regression of endometrial implants in a rat model of endometriosis without affecting fertility. *European Journal of Pharmacology*, 702(1-3):12-19.
- Amsterdam, L. L., Gentry, W., Jobanputra, S., Wolf, M., Rubin, S. D., Bulun, S. E. 2005. Anastrozole and oral contraceptives: a novel treatment for endometriosis. *Fertility and Sterility*, 84(2):300-304.
- Amuthan, A., Anandh, S., Musharraf, S., Agarwal, N., Devi, V., Shenoy, R. P., Nayal, B. 2016. Effect of Notchi kudineer (Vitex negundo aqueous extract) on surgically induced Endometriosis in Sprague Dawley rats. *International Journal of Pharmacology and Clinical Sciences*, 4(3):35-43.
- Bensky, D., Clavey, S., Stoger, E. 2004. Chinese Herbal Medicine: Materia Medica. Eastland Press. 3rd ed. ed; Eastland Press, Seattle.
- Chen, R., Liu, H., Jiang, R., Li, X., Qu, Y. F. 2010. Effect of traditional Chinese medicine (Daqiqi Tang) on expressions of VEGF and MMP-9 in endometriosis rats. *Reproduction & Contraception*, 30(10):659-663.
- Cheng, W., Chen, L., Yang, S., Han, J., Zhai, D., Ni, J., Yu, C., Cai, Z. 2012. Puerarin Suppresses Proliferation of Endometriotic Stromal Cells Partly via the MAPK Signaling Pathway Induced by 17 β -estradiol-BSA. *PLoS One*, 7(9):e45529.
- Collins, N. H., Lessey, E. C., DuSell, C. D., McDonnell, D. P., Fowler, L., Palomino, W. A., Illera, M. J., Yu, X.,

- Mo, B., Houwing, A. M., Lessey, B. A. 2009. Characterization of Antiestrogenic Activity of the Chinese Herb, *Prunella vulgaris*, Using In Vitro and In Vivo (Mouse Xenograft) Models. *Biology of Reproduction*, 80(2):375–383.
- Demirel, M. A., Suntar, I., Ilhan, M., Keles, H., Akkol, E. K. 2014. Experimental endometriosis remission in rats treated with *Achillea biebersteinii* Afan.: histopathological evaluation and determination of cytokine levels. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, 175:172–177.
- Edwards, A. K., Nakamura, D. S., Virani, S., Wessels, J. M., Tayade, C. 2013. Animal models for anti-angiogenic therapy in endometriosis. *Journal of Reproductive Immunology*, 97(1):85–94.
- Fantasia, H. C. 2019. Elagolix as a Novel Treatment for Endometriosis-Related Pain. *Nursing for Women's Health*, 23(4):366–369.
- Ferella, L., Bastón, J. I., Bilotas, M. A., Singla, J. J., González, A. M., Olivares, C. N., Meresman, G. F. 2018. Active compounds present in *Rosmarinus officinalis* leaves and *Scutellaria baicalensis* root evaluated as new therapeutic agents for endometriosis. *Reproductive BioMedicine Online*, 37(6):769–782.
- Gibrán, L., Maranhão, R. C., Abrão, M. S., Baracat, E. C., Podgaec, S. 2014. Could statins constitute a novel treatment for endometriosis? Systematic review of the literature. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, 179:153–158.
- Guo, S. W. 2015. Endometriosis and ovarian cancer: potential benefits and harms of screening and risk-reducing surgery. *Fertility and Sterility*, 104(4):813–830.
- Haghi, A., Azimi, H., Rahimi, R. 2017. A Comprehensive Review on Pharmacotherapeutics of Three Phytochemicals, Curcumin, Quercetin, and Allicin, in the Treatment of Gastric Cancer. *Journal of Gastrointestinal Cancer*, 48(4):314–320.
- Harada, T., Kosaka, S., Elliesen, J., Yasuda, M., Ito, M., Momoeda, M. 2017. Ethinylestradiol 20 µg/drospirenone 3 mg in a flexible extended regimen for the management of endometriosis-associated pelvic pain: a randomized controlled trial. *Fertility and Sterility*, 108(5):798–805.
- Hisa, T., Kimura, Y., Takada, K., Suzuki, F., Takigawa, M. 1998. Shikonin, an ingredient of *Lithospermum erythrorhizon*, inhibits angiogenesis in vivo and in vitro. *Anticancer Research*, 18(2A):783–790.
- Ivanov, V., Ivanova, S., Kalinovskiy, T., Niedzwiecki, A., Rath, M. 2008. Plant-Derived Micronutrients Suppress Monocyte Adhesion to Cultured Human Aortic Endothelial Cell Layer by Modulating Its Extracellular Matrix Composition. *Journal of Cardiovascular Pharmacology*, 52(1):55–65.
- Jha, U., Asad, M., Asdaq, S. M. B., Das, A. K., Prasad, V. S. 2010. Fertility inducing effect of aerial parts of *Coccinia cordifolia* L. in female rats. *Journal of Ethnopharmacology*, 127(2):561–564.
- Jiang, D., Li, L., Zeng, B. Y. 2017. Treatment of Chinese Herbal Medicine for Female Infertility. *International Review of Neurobiology*, pages 233–247.
- Jin, Z., Huang, J., Zhu, Z. 2017. Baicalein reduces endometriosis by suppressing the viability of human endometrial stromal cells through the nuclear factor- κ B pathway in vitro. *Experimental and Therapeutic Medicine*, 14(4):2992–2998.
- Jr, H. M., Haddad, Pinheiro, Casoy 2012. Advantages of the association of resveratrol with oral contraceptives for management of endometriosis-related pain. *International Journal of Women's Health*, 4:543–543.
- Kim, H. W., Yoo, J. E. 2018. Inhibitory effect of traditional Korean medicine on the recurrent endometriosis after laparoscopic excision: a case report. *Integrative medicine research*, 7(3):296–301.
- Kim, J. H., Jung, S. H., Yang, Y. I., Ahn, J. H., Cho, J. G., Lee, K. T., Baek, N. I., Choi, J. H. 2013a. Artemisia leaf extract induces apoptosis in human endometriotic cells through regulation of the p38 and NF κ B pathways. *Journal of Ethnopharmacology*, 145(3):767–775.
- Kim, K. H., Park, J. K., Choi, Y. W., Kim, Y. H., Lee, E. N., Lee, J. R., Kim, H. S., Baek, S. Y., Kim, B. S., Lee, K. S., Yoon, S. 2013b. Hexane extract of aged black garlic reduces cell proliferation and attenuates the expression of ICAM-1 and VCAM-1 in TNF- α -activated human endometrial stromal cells. *International Journal of Molecular Medicine*, 32(1):67–78.
- Kohama, T., Herai, K., Inoue, M. 2007. Effect of French maritime pine bark extract on endometriosis as compared with leuprorelin acetate. *The Journal of Reproductive Medicine*, 52(8):703–708.
- Lin, L. G., Liu, Q. Y., Ye, Y. 2014. Naturally occurring homoisoflavonoids and their pharmacological activities. *Planta medica*, 80(13):1053–1066.
- Long, J. R., Li, Z. 2012. Ginsenoside Rg3 in combination with surgery in patients with stage III-IV endometriosis: a clinical control trial. *Chinese Remedies & Clinics*, 12(6):720–724.
- Machado, D. E., Rodrigues-Baptista, K. C., Alessandra-Perini, J., de Moura, R. S., dos Santos,

- T. A., Pereira, K. G., da Silva, Y. M., Souza, P. J. C., Nasciutti, L. E., Perini, J. A. 2016. Euterpe oleracea Extract (Açaí) Is a Promising Novel Pharmacological Therapeutic Treatment for Experimental Endometriosis. *PloS One*, 11(11):e0166059.
- Melki, E. 2019. Endometriosis treatment with shock waves: A novel approach. *Medical Hypotheses*, 124:114–117.
- Neto, J. N., Coelho, T. M., Aguiar, G. C., Carvalho, L. R., de Araújo, A. G. P., Girão, M. J. B., Schor, E. 2011a. Experimental endometriosis reduction in rats treated with *Uncaria tomentosa* (cat's claw) extract. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, 154(2):205–208.
- Neto, N., Lindoso, J., De, M. J., Coelho, S., Carvalho, L. F., Rodrigues, R. A. F., De, T. G. P., Araújo, M., De, A. G. P., Girão, M. J. B. C., Schor, E. 2011b. Changes in the volume and histology of endometriosis foci in rats treated with copaiba oil (*Copaifera langsdorffii*). *Acta Cirurgica Brasileira*, 26(Suppl 2):20–24.
- Paola, R. D., Fusco, R., Gugliandolo, E., Crupi, R., Evangelista, M., Granese, R., Cuzzocrea, S. 2016. Co-micronized Palmitoylethanolamide/Polydatin Treatment Causes Endometriotic Lesion Regression in a Rodent Model of Surgically Induced Endometriosis. *Frontiers in Pharmacology*, 7.
- Park, K. S. 2019. The Efficacy and Safety of Korean Herbal Medicine in a Patient with Endometrioma of The Ovary: A Case Report. *Explore*, 15(2):142–147.
- Park, S., Lim, W., Bazer, F. W., Song, G. 2018. Apigenin induces ROS-dependent apoptosis and ER stress in human endometriosis cells. *Journal of Cellular Physiology*, 233(4):3055–3065.
- Qinshu, Z., Yi, F., Li, W., Rong, C. 2012. Effect of Da Qiqi decoction on expression of P450 and COX-2 in endometriosis of rats. *Journal of Third Military Medical University*, 34(21):2167–2170.
- Rivera, R., Yacobson, I., Grimes, D. 1999. The mechanism of action of hormonal contraceptives and intrauterine contraceptive devices. *American Journal of Obstetrics and Gynecology*, 181(5):1263–1269.
- Rojas-Duran, R., González-Aspajo, G., Ruiz-Martel, C., Bourdy, G., Doroteo-Ortega, V. H., Alban-Castillo, J., Robert, G., Auberger, P., Deharo, E. 2012. Anti-inflammatory activity of *Mitraphylline* isolated from *Uncaria tomentosa* bark. *Journal of Ethnopharmacology*, 143(3):801–804.
- Rudzitis-Auth, J., Korbil, C., Scheuer, C., Menger, M. D., Laschke, M. W. 2012. Xanthohumol inhibits growth and vascularization of developing endometriotic lesions. *Human Reproduction*, 27(6):1735–1744.
- Saltan, G., Süntar, I., Ozbilgin, S., Ilhan, M., Demirel, M. A., Oz, B. E., Keleş, H., Akkol, E. K. 2016. *Viburnum opulus* L.: A remedy for the treatment of endometriosis demonstrated by rat model of surgically-induced endometriosis. *Journal of Ethnopharmacology*, 193:450–455.
- Sharma, M., Schoop, R., Hudson, J. B. 2009. Echinacea as an anti-inflammatory agent: the influence of physiologically relevant parameters. *Phytotherapy Research*, 23(6):863–867.
- Stanilova, M., Gorgorov, R., Trendafilova, A., Nikolova, M., Vitkova, A. 2012. Influence of Nutrient Medium Composition on in vitro Growth, Polyphenolic Content and Antioxidant Activity of *Alchemilla mollis*. *Natural Product Communications*, 7(6):1934578X1200700.
- Takai, E., Taniguchi, F., Nakamura, K., Uegaki, T., Iwabe, T., Harada, T. 2013. Parthenolide reduces cell proliferation and prostaglandin estradiol synthesis in human endometriotic stromal cells and inhibits development of endometriosis in the murine model. *Fertility and Sterility*, 100(4):1170–1178.
- Tanaka, T., Umesaki, N., Mizuno, K., Fujino, Y., Ogita, S. 2000. Anti-endometrial IgM autoantibodies in endometriotic patients: a preliminary study. *Clinical and experimental obstetrics & gynecology*, 27(2):133–137.
- Vercellini, P., Buggio, L., Berlanda, N., Barbara, G., Somigliana, E., Bosari, S. 2016. Estrogen-progestins and progestins for the management of endometriosis. *Fertility and Sterility*, 106(7):1552–1571.e2.
- Vercellini, P., Trespido, L., Colombo, A., Vendola, N., Marchini, M., Crosignani, P. G. 1993. A gonadotropin-releasing hormone agonist versus a low-dose oral contraceptive for pelvic pain associated with endometriosis. *Fertility and Sterility*, 60(1):75–79.
- Vercellini, P., Viganò, P., Somigliana, E., Fedele, L. 2014. Endometriosis: pathogenesis and treatment. *Nature Reviews Endocrinology*, 10(5):261–275.
- Wang, S. R., Guo, Z. Q., Liao, J. Z. 1993. Experimental study on effects of 18 kinds of Chinese herbal medicine for synthesis of thromboxane A2 and PGI2. *Chinese Journal of Integrated Traditional and Western Medicine*, 13(3):167–170.
- Wichtl, M. 2004. Herbal drugs and phytopharmaceuticals: A handbook for practice on a scientific basis. 4th ed., ISBN: 3887631005.
- Wu, Y., Wang, L. P., Pan, J. Q. 2011. Nicotinic

- acetylcholine receptor agonists may be a novel therapy for endometriosis. *Medical Hypotheses*, 77(5):745-747.
- Xiao, Y. H., Chen, D. P., Yan, J. H., Yokoyama, Y. 2002. Mechanism of action of Tripterygium Wilfordii polyglycoside on experimental endometriosis. *European Journal of Gynaecological Oncology*, 23(1):63-67.
- Xu, H., Becker, C. M., Lui, W. T., Chu, C. Y., Davis, T. N., Kung, A. L., Wang, C. C. 2011. Green tea epigallocatechin-3-gallate inhibits angiogenesis and suppresses vascular endothelial growth factor C/vascular endothelial growth factor receptor 2 expression and signaling in experimental endometriosis in vivo. *Fertility and sterility*, 96(4):1021-1028.
- Zhang, X., Zhang, L., Wang, Q., Sun, X., Dong, Y., Xing, Y., Ma, X. 2019. Exploration of the potential mechanism of Danggui Shaoyao powder in the treatment of endometriosis based on bioinformatics. *Journal of Traditional Chinese Medical Sciences*, 6(4):355-364.
- Zheng, W., Cao, L., Xu, Z., Ma, Y., Liang, X. 2018. Anti-Angiogenic Alternative and Complementary Medicines for the Treatment of Endometriosis: A Review of Potential Molecular Mechanisms. *Evidence-Based Complementary and Alternative Medicine*, 2018:1-28.
- Zhou, Z. H., Weng, Q., Zhou, J. H., Zhou, J. 2012. Extracts of *Salvia miltiorrhiza bunge* on the cytokines of rat endometriosis models. *African Journal of Traditional, Complementary and Alternative Medicines*, 9(3):303-314.