

Therapeutic Potential of Natural Resources Against Endometriosis: Current Advances and Future Perspectives

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Abstract: Endometriosis (EMS) is defined as the appearance, growth, infiltration, and repeated bleeding of endometrioid tissue (glands and stroma) outside the uterus cavity, which can form nodules and masses. Endometriosis is a chronic inflammatory estrogen-dependent disease and occurs in women of reproductive age. This disorder may significantly affect the quality of life of patients. The pathogenic processes involved in the development and maintenance of endometriosis remain unclear. Current treatment options for endometriosis mainly include drug therapy and surgery. Drug therapy mainly ties to the use of non-steroidal anti-inflammatory drugs (NSAIDs) and hormonal drugs. However, these drugs may produce adverse effects when used for long-term treatment of endometriosis, such as nausea, vomiting gastrointestinal reactions, abnormal liver and kidney function, gastric ulcers, and thrombosis. Although endometriosis lesions can be surgically removed, the disease has a high recurrence rate after surgical resection, with a recurrence rate of 21.5% within 2 years and 40% to 50% within 5 years. Thus, there is an urgent need to develop alternative or additional therapies for the treatment of endometriosis. In this review, we give a systematic summary of therapeutic multiple component prescriptions (including traditional Chinese medicine and so on), bioactive crude extracts of plants/herbs and purified compounds and their newly found mechanisms reported in literature in recent years against endometriosis.

Keywords: endometriosis, treatment, multiple component prescriptions, extracts of plants/herbs, purified compounds, mechanisms

Introduction

The definition of endometriosis (EMS) is the presence of endometrial tissue outside of the uterine cavity. It is considered as an estrogen-dependent chronic inflammatory disorder that primarily affects pelvic organs, including the ovaries. Although endometriosis is one of the most common benign gynecological disorders, the pathogenesis of endometriosis remains unclear. To date, several theories have been established to explain the origination of endometriosis, the most popular and widely accepted one is Sampson's retrograde menstruation theory.¹ It is now widely accepted that the onset and progression of this disease are associated with estrogen dominance and progesterone resistance,² a pro-inflammatory pelvic microenvironment,³ increased neovascularization,⁴ apoptosis dysregulation,⁵ cell proliferation dysregulation,⁶ fibrosis,⁷ migration,⁸ invasion,⁹ dysregulation of oxidative stress and anti-oxidative stress,¹⁰ and alterations in epigenetic factors¹¹ (Figure 1). Endometriosis can spread like a sandstorm in the ovaries, fallopian tubes, pelvic cavity and intestines. The clinical manifestations include chronic pelvic pain, dysuria, progressively increasing dysmenorrhea, gastrointestinal symptoms, painful intercourse, painful bowel movements during menstruation, infertility, and irregular menstruation.^{12–17} Based on the histopathology and anatomic location of endometriosis, it can be classified into four subtypes: ovarian endometriosis, superficial endometriosis, deep infiltrative endometriosis (DIE),¹⁸ and other sites of endometriosis.¹⁹ Current clinical options for the treatment of endometriosis mainly include

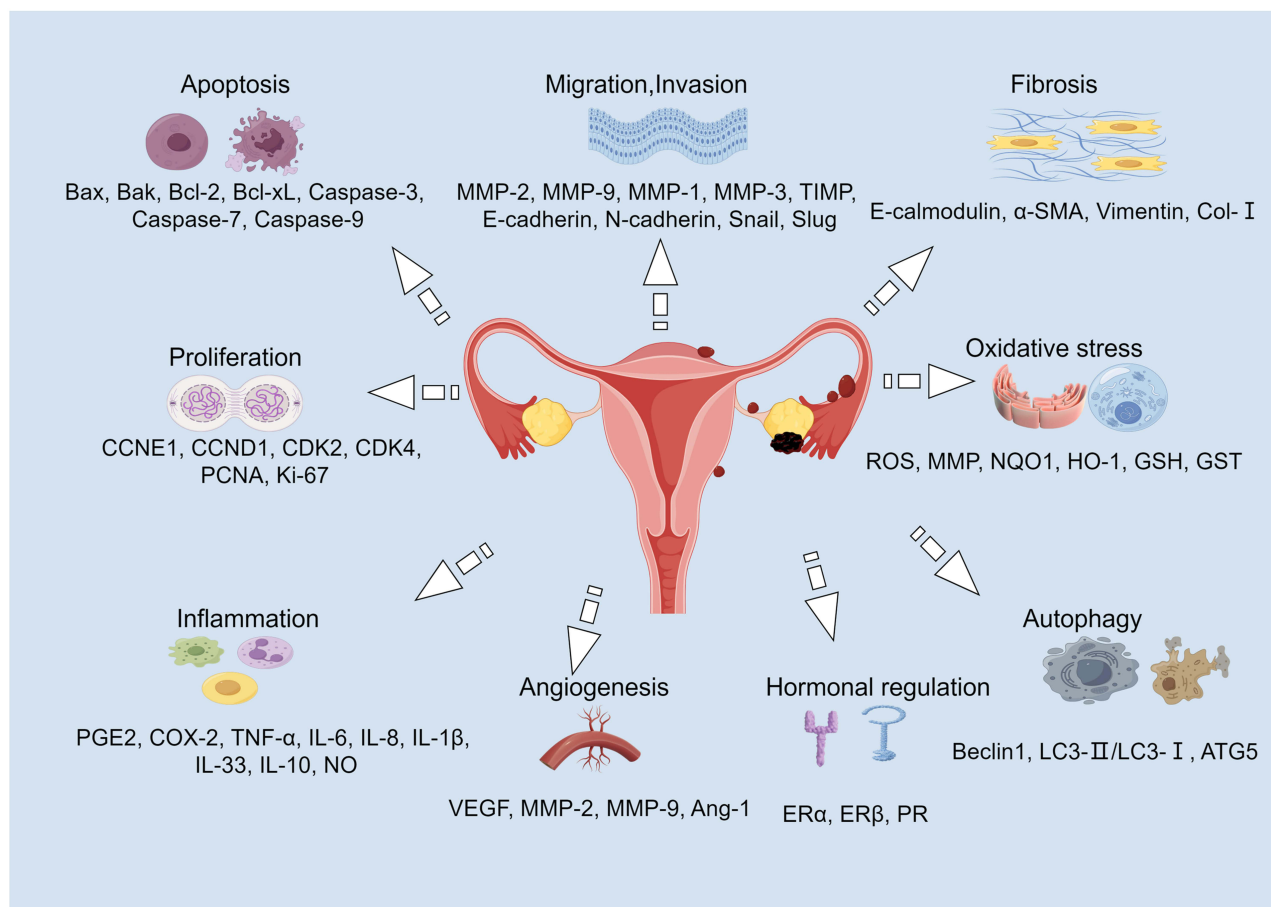


Figure 1 Molecular mechanisms and factors involved in the occurrence and development of endometriosis.

pharmacological and surgical treatments. The following drugs are commonly used for the treatment of endometriosis: non-steroidal anti-inflammatory drugs (NSAIDs),^{20,21} combined oral contraceptives pills (COCP),^{22,23} progesterone,²⁴ mifepristone (selective progesterone receptor modulators, SPRM),²⁵ danazol (pseudo-menopausal therapy),²⁶ gonadotropin-releasing hormone agonist (GnRH-a),²⁷ aromatase inhibitors,²⁸ gonadotropin-releasing hormones (GnRH) antagonists.^{29,30} These drugs often generate serious adverse effects when used for long-term treatment of endometriosis, such as nausea, vomiting gastrointestinal reactions, abnormal liver and kidney function, gastric ulcers, thrombosis, depression, headache, breast tenderness, weight gain, irregular spotting of vaginal bleeding and dryness, hot flashes, loss of libido and bone.^{22,24–28,30–32} In addition, drug therapy is ineffective in some patients. The specific mechanisms of action and adverse side effects of the mentioned drugs are shown in [Table S1](#). The purpose of surgical treatment is to remove endometriotic lesions and restore the normal anatomical structure. When the symptoms are not relieved after drug treatment, the local lesions are aggravated, the fertility function is not recovered, and the ovarian endometriosis cysts are larger, it is suitable for surgical treatment. The surgical methods mainly include fertility-preserving surgery, ovary-preserving surgery, and radical surgery ([Table S2](#)).²⁹ Clinically, few patients choose radical surgery, and almost all patients choose fertility-preserving surgery, which may lead to a high postoperative recurrence rate. Unlike other ovarian cysts, ovarian chocolate cysts are firmly adherent to the ovarian cortex and stroma, which can make surgical removal of the ovarian cyst wall difficult and lead to inadvertent removal of normal ovarian tissue, ultimately resulting in decreased ovarian reserve function. Even though endometriosis lesions can be surgically removed, the recurrence rate is high, with a 2-year recurrence rate of 21.5% and a 5-year recurrence rate of 40% - 50%.³³ Surgery remains the gold standard for the final diagnosis, but the risks of surgery must be weighed against the potential decrease in ovarian reserve, especially in the case of bilateral endometriomas and previous ovarian surgery.^{31,34} Obviously, the current clinical drug therapy and surgical treatment have been

unable to meet the individual treatment needs of patients with endometriosis. Therefore, there is an urgent need to develop new drugs that can achieve higher efficacy, fewer side effects and can be used as long-term treatment options.

Some therapeutic mixtures or crude preparations made from natural materials, especially from plants, have been used to combat diseases for a long time in human history. The basis of these synergistic effects of the mixtures or crude preparations is bioactive ingredients. With the development of antibiotics in the mid-twentieth century, purified compounds have become more typical in drug formulations. These compounds obtained from natural sources, eg, plants, animals, minerals, and microorganisms, are grouped as natural products (NPs) scientifically. In order to adapt to the environment and improve the competitiveness of survival, organisms interact with the environment to form extremely complex chemical structures in the body after hundreds of millions of years of evolution. These molecules may increase their competitive advantages in the ecosystem in which they operate.³⁵ Natural products have long been a source of new drug development.³⁶ First of all, the use of natural products as “as they are” to treat various diseases has been extensively documented in literature and books since ancient times. Secondly, with the development of industrial technology and the progress of drug development, it has become possible to extract and isolate components with clear structures and special biological activities from plants.³⁷ Moreover, these compounds with clear structures and special biological activities have great potential to be modified. According to the needs of clinical medication, some of its structure can be changed emphatically, so as to improve the characteristics of such compounds.³⁸ Thus, natural products can be used as a powerful pool to produce new therapeutic drugs.³⁶

In this review, a literature search was conducted in the database of Pubmed and Medline. Various terms “endometriosis”, “treatment”, “medication”, “natural product”, “herb/herbal”, “extract”, “phytochemical”, “compound” and “bioactive compound” were used as key words for relevance. The articles were published in English from 2017 to 2023 and were original ones. This review is divided into three parts, namely, multiple component prescriptions (including traditional Chinese medicine and so on), crude extracts of plants/herbs, and purified bioactive compounds and their newly found mechanisms reported in literature against endometriosis.

Multiple Component Prescriptions

Cai's Neiyi Prescription (CNYP)

Cai's Neiyi Prescription (CNYP) is created by professor Xiaosun Cai from China. Based on Gui Zhi Fu Ling Pill, CNYP is mixed with shanjiaopian (pangolin tablets), zhaojiaoci (spina gleditsiae), and eshu (rhizoma curcumae). Cai's Neiyi Prescription mainly consists of the following traditional Chinese medicine, baifuling (chinaroot greenbrier rhizome), guizhi (cassia twig), shuizhi (leech), chishao (radix paeoniae rubra), eshu (rhizoma curcumae), shijianchuan (Chinese sage herb), mudanpi (cortex moutan), zhaojiaoci (spina gleditsiae), taoren (peach seed) (Table S3).³⁹ Li et al found that Cai's Neiyi Prescription reduced the expression of interleukin-1 β (IL-1 β), IL-6, transforming growth factor- β (TGF- β), and tumor necrosis factor- α (TNF- α) in human endometriotic stromal cells and rat model of endometriosis with autologous transplantation. In addition, CNYP could reduce the expression of anti-apoptotic protein B-cell lymphoma-2 (Bcl-2), and also could upregulate the expression of pro-apoptotic proteins Bcl-2 associated X protein (Bax) and caspase-7 by inhibiting the activation of the ERK/2 signaling pathway.⁴⁰ In conclusion, CNYP may exert anti-endometriosis effects by inhibiting the inflammatory response and promoting apoptosis.

Danefukang Jianga

Danefukang Jianga (DEFK) is a common Chinese patent medicine for the treatment of endometriosis and adenomyosis, which has the effects of activating blood circulation, regulating menstruation, relieving pain, and softening and dispersing nodules.⁴¹ DEFK mainly contains radix salviae miltiorrhizae, rhizoma curcumae, sanleng, rhizoma cyperi, rhizoma corydalis (Table S3).⁴² Zhong et al randomly divided 174 patients with endometriosis into an experimental group (DEFK group) and a control group (mifepristone group), with 87 patients in each group. The levels of inflammatory cytokines (TNF- α , IL-6), and carbohydrate antigen-125 (CA-125) were significantly downregulated in the DEFK group. The patients in DEFK group also showed a higher quality of life (QOL) scores, a lower depression and anxiety self-assessment scale (SDS and SAS) scores compared with the control group (mifepristone).⁴³

Guizhi Fuling Decoction

Guizhi fuling Decoction (GZFLD) is one of the classic Chinese herbal prescriptions, mainly used to treat gynecological diseases. The prescription of GZFLD consists of five herbs: poria cocos, persicae semen, paeoniae radix, cinnamon cortex, and moutan cortex (Table S3).⁴⁴ Gao et al predicted the potential signaling pathways and targets of GZFLD in the treatment of endometriosis through bioinformatics methods. Further experiments were carried out in vitro and in vivo. According to the results, GZFLD could reduce the expression of inflammatory cytokines (IL-6, IL-1 β , TNF- α) in ectopic endometriosis rat model. Meanwhile, the effect of GZFLD on hyperalgesia was supported by a hot plate experiment. What's more, the nerve fiber density of ectopic endometrial tissue of rats was reduced after the treatment of GZFLD. They hypothesized that GZFLD might relieve endometriosis related pain by reducing the nerve fiber density and exert anti-inflammatory effects through the downregulation of the PI3K/Akt signaling pathway.⁴⁵

Huangzhi Neiyi Capsule

Huangzhi Neiyi Capsule (HZNYC) is a Chinese medicinal preparation developed by professor Min Xia of Chongqing Hospital of Traditional Chinese Medicine and is mostly used clinically for the treatment of endometriosis. HZNYC is mainly composed of three traditional Chinese medicines, namely, cooked rhubarb, leech, and Cyperus rotundus, which have the functions of activating blood circulation, resolving blood stasis, and relieving pain (Table S3).⁴⁶ Vascularization plays a vital role in the pathogenesis of endometriosis by providing nutrients and oxygen for the growth of endometriotic lesions. Neovascularization of endometriotic lesions, including angiogenesis, vasculogenesis, and inosculation, is a complex process. Neovascularization involves several growth factors and cytokines, such as fibroblast growth factor (FGF), platelet-derived endothelial cell growth factor (PD-ECGF), angiopoietin (Ang)1/2, matrix metalloproteinase-2 (MMP-2) and matrix metalloproteinase-9 (MMP-9), among which vascular endothelial growth factor (VEGF) is the most vital irritant.⁴ Ectopic endometrium is in a hypoxic environment during ectopic implantation. Under hypoxic conditions, hypoxia-inducible factor-1 alpha (HIF-1 α) fails to undergo ubiquitination and degradation, then undergoes nuclear translocation to bind to promoters on the vascular endothelial growth factor gene, finally increasing the expression of HIF-1 α and VEGF in endometriotic lesions.⁴⁷ Liu et al found that HZNYC could reduce the expression of mRNA of HIF-1 α by regulating the HIF-1 α /VEGF signaling pathway, which in turn reduced the expression of VEGF in the peritoneal fluid and endometriotic lesions of Sprague-Dawley (SD) rats endometriosis model.⁴⁸ In conclusion, HZNYC inhibits the progress of endometriosis by suppressing neovascularization.

NeiyiKangfu Tablet

NeiyiKangfu Tablet (NYKFT) is a traditional Chinese preparation made by the Affiliated Hospital of Chengdu University of Traditional Chinese Medicine. The preparation is mainly composed of bichihua, sanguoteng, cooked rhubarb, peach kernel, three prune, coix seed, soil turtle worm, turtle, and other medicinal materials (Table S3). It mainly has the effects of clearing dampness and removing blood stasis, dispersing knot, and relieving pain.⁴⁹ Raf kinase inhibitory protein (RKIP) is a widely expressed negative regulator of the RAF/MEK/ERK signaling pathway. By directly binding RAF-1 and MEK, RKIP interferes with the formation of the kinase-substrate complex, thereby inhibiting the phosphorylation of MEK, ultimately plays a role in inhibiting RAF/MEK/ERK signaling pathway. It is well known that the RAF/MEK/ERK pathway plays a key role in controlling cell proliferation and protecting cells from apoptosis.^{49,50} Wen et al demonstrated that NYKFT could promote the expression of Raf kinase inhibitory protein in a dose-dependent manner in vivo and in vitro. The upregulated expression of RKIP inhibited the RAF/MEK/ERK signaling pathway, resulting in the increased expression of Bax and cleaved caspase-3, and the decreased expression of Bcl-2. In addition, NYKFT treatment decreased the secretion of pro-inflammatory cytokines IL-6 and TNF- α in EMS mice compared with the control group.⁵¹

Neiyi Prescription of QIU

Neiyi Prescription of QIU (NYPQ) was founded by the late professor Xiaomei Qiu, a famous Chinese doctor. NYPQ is mainly used to treat endometriosis and adenomyosis. It has the effects of dispersing knot and relieving pain, promoting blood circulation, and removing blood stasis. It consists of the following components: baristellia, honeysuckle vine, red

vine, *Prunella japonicus*, *hedyotis vulgaris*, white hair vine, *corydalis yanhusuo*, purple salvia *miltiorrhiza*, willebrand, barley malt, fried hawthorn, fragrant tea vegetable, conch mountain (Table S3).⁵² Autophagy and angiogenesis are important processes in the development of endometriosis.^{4,53} Angiogenesis provides nutritional support for the implantation, proliferation, and survival of endometriotic lesions. It is widely believed that the growth of neovascularization is closely related to vascular endothelial growth factor. Beclin 1 and light chain 3 (LC3) are both specific markers of autophagy. Under normal conditions, LC3 protein is present in the cytoplasm as type I. When autophagy is activated, LC3-I is recruited to autophagosomes and subsequently converted to LC3-II.⁵⁴ Therefore, the level of autophagy could be assessed by comparing the amount of LC3-II or the ratio of LC3-II to LC3-I. Yang et al demonstrated that NYPQ could exert an antiangiogenic effect by reducing VEGF expression in a rat model of surgically induced endometriosis. In addition, NYPQ could induce cell apoptosis by promoting the expression of autophagy-related protein Beclin 1, and by increasing the amount of LC3-II or the ratio of LC3-II/I, ultimately inhibiting the progression of endometriotic lesions. In addition, they observed that NYPQ could promote the apoptosis of human umbilical vein endothelial cells (HUVECs) and inhibit the tubular formation of HUVECs by flow cytometry and lumen formation assay. Anti-angiogenesis and apoptotic effects of NYPQ might be achieved through the activation of the PPAR γ /nuclear factor kappa B (NF- κ B) signaling pathway.⁵⁵

Shaofu Zhuyu Decoction

Shaofu Zhuyu Decoction (SZD) is one of the common herbal formulas for the treatment of dysmenorrhea, with the effect of invigorating blood circulation and eliminating blood stasis, warming menstruation, and relieving pain. It consists of ten herbs: *zingiberis rhizoma*, *cortex cinnamomi*, *corydalis rhizoma*, *trogopteri feces*, *angelicae sinensis radix*, *fructus radix paeoniae rubra*, *typhae pollen*, *myrrha*, *rhizoma chuanxiong*, and *foeniculi* (Table S3).⁵⁶ Zhu et al showed that cell proliferation was inhibited, while apoptosis was promoted after SZD was applied to rats with endometriosis. Moreover, SZD treatment reduced the expression level of HIF-1 α and its subsequent transcriptional target VEGF, which in turn reduced the angiogenesis and decreased the volume of endometriotic lesions.⁵⁷

Tokishakuyakusan

Tokishakuyakusan (TSS) is a Japanese traditional herbal medicine. TSS consists of six herbal components including *lanceae rhizoma*, *cnidii rhizoma*, *paeoniae radix*, *angelicae*, *atractylodis*, and *hoelen* (Table S3).⁵⁸ Nagira et al observed that TSS inhibited the development of endometriotic lesions in surgically induced BALB/c mice. And the expression of IL-33 mRNA was decreased after the treatment of TSS. Through hot plate assay, they also demonstrated that TSS alleviated hyperalgesia in a mouse model of endometriosis.⁵⁹ Takeuchi et al illustrated that TSS and one of its components, ferulic acid (FA), reduced IL-8 and VEGF production in human endometrial stromal cells (HESCs).⁶⁰ In conclusion, TSS inhibits the progress of endometriosis due to anti-inflammatory and anti-angiogenic pharmacological activities.

Crude Extracts of Plants/Herbs

Achillea Cretica L. Aerial Extract

Achillea cretica L. (AC) is a medicinal plant. The extract of AC mainly consists of flavonoids and phenolic acids. Bina et al found that the extract of AC could reduce the volume of ectopic endometrial lesions on a rat model of endometriosis. Furthermore, the expression levels of inflammatory factors (IL-6, TNF- α) and VEGF were decreased.⁶¹

Basil (*Ocimum Basilicum* L.) Leaves Extract

Basil (*Ocimum basilicum* L.) leaves contain high levels of flavonoids. The extract of basil leaves exhibited anti-proliferative, anti-inflammatory, and antioxidant activities.⁶² By establishing a mouse model of endometriosis, A'Yuni et al demonstrated that basil leaves extract could inhibit the progression of endometriosis by reducing the expression of VEGF in the vascular endothelium of endometriosis tissues.⁶³

Boswellia Serrata Extract

Boswellia serrata (BS) belongs to a branch of the family Burseraceae. *Boswellia serrata* is well documented for its anti-inflammatory activity.⁶⁴ Most of its biological activity is attributed to pentacyclic triterpenoids. Nuclear factor red lineage related factor 2 (Nrf2) regulates the transcription of endogenous antioxidant enzymes. Under basal conditions, the Kelch-like ECH-associated protein 1 (Keap1) forms a complex with Nrf2, leading to ubiquitination and subsequent degradation of Nrf2. Under conditions of oxidative stress, Keap1-CUL3-E3 ubiquitin ligase undergoes conformational changes, which disrupt the binding of Nrf2 to Keap1. Free Nrf2 translocates to the nucleus and transcribes antioxidant enzyme genes, NAD(P)H quinone oxidoreductase (NQO1) and heme oxygenase-1 (HO-1).⁶⁵ R. D'Amico et al demonstrated that after the treatment of BS gum resin extract on the Sprague-Dawley rat model of endometriosis, the expression of Nrf2, HO-1, and NQO-1 proteins in ectopic lesions was increased compared with that of the model group. The study also demonstrated that oral BS gum resin extract therapy could reduce Bcl-2 expression and increase the level of Bax in ectopic endometrial lesions. Moreover, it could increase the cleavage rate of caspase-9 and the cleavage of apoptotic marker PARP.⁶⁶

Calligonum Comosum (Escanbil) Extract

Calligonum comosum (Escanbil) is a plant that mainly grows in desert areas,⁶⁷ with various pharmacological activities, such as anti-proliferation, pro-apoptosis,⁶⁸ anti-oxidation,⁶⁹ anti-cancer⁷⁰ and anti-inflammation.⁷¹ Kiani's team demonstrated that *Calligonum comosum* extract could inhibit the migration and tubular formation of human dermal microvascular endothelial cells (HDMEC). *Calligonum comosum* extract inhibited the growth of ectopic endometrial lesions, the formation of blood vessels and the infiltration of immune cells (macrophages and lymphocytes) in the animal model.⁷²

Cyperi Rhizoma Extract

Cyperi rhizome is a medicinal plant, belonging to the rhizome of *Cyperus rotundus* L. Cyperi rhizome grows naturally all over the world, especially in tropical, subtropical, and temperate regions. Cyperi rhizome is also a common traditional Chinese herbal medicine.⁷³ Cyperi rhizoma extract (CRE) exhibits a wide range of biological properties, including anti-inflammatory, anti-platelet, antioxidant, pro-apoptotic, anti-proliferative, and estrogenic properties.^{74–77} The adhesion molecules p-calmodulin and MMP-2 are involved in the regulation of cell-cell adhesion, cell-ECM adhesion, and adhesion of endometriotic cells and peritoneal mesothelial cells during the development of endometriosis. In addition, their expression is upregulated in endometriotic lesions.^{78–80} Neurotrophins, a family of nerve growth factors, such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophic factor 3 (NT-3), and neurotrophic factor 4/5 (NT-4/5), are considered to be endometriosis-associated pain factors. These factors are overexpressed in endometriosis.⁸¹ Ahn et al demonstrated that CRE could significantly downregulate the mRNA expression of the adhesion molecules p-cadherin and MMP-2 in 12Z cells. In addition, the mRNA expression of neurotrophins such as BDNF, NGF, NT-3, and NT-4/5 was significantly decreased after the treatment with CRE in 12Z cells. CRE inhibited the progression of endometriosis through the regulation of the Akt and NF- κ B pathways.⁸²

Extract of Polygala Fallax Hemsl

Polygala fallax Hemsl (PFH) is generally recognized as a unique edible and medicinal plant in China. In the Guilin city of Guangxi province of China, people often stew their roots with meat to treat endometriosis as a dietary therapy.⁸³ Zhong's team isolated and cultured human ectopic endometrial stromal cells (HEcESCs) from fresh ectopic endometrial tissue (ovarian endometrial tumor wall) of patients diagnosed with ovarian endometriosis. Through flow cytometry, Western blotting, transwell assay and some other experiments, they found that PFH extract (total flavonoids of *Polygala fallax* Hemsl, PFHF) could inhibit the proliferation, migration, invasion, and promote apoptosis of HEcESCs by inhibiting the PI3K/Akt signaling pathway.⁸⁴

Pueraria Flower Extract

Pueraria lobata is a basic traditional Chinese herb. *Pueraria* flower is rich in isoflavones. Its health benefits partially may be due to isoflavones in the extract.^{85–87} Kim et al showed that *pueraria* flower extract (PFE) exposure attenuated the adhesion of immortalized human endometriotic cells (11Z and 12Z cells) to human mesothelial cells Met5A. Furthermore, treatment with PFE significantly inhibited 11Z and 12Z cells migration through scratch (wound healing) assay and transwell-migration assay.⁸⁸ Previous relevant studies showed that MMP-2 and MMP-9 play a critical role in the progression of adhesion, invasion, and neovascularization of ectopic endometrial tissue.^{79,80,89} The protein and mRNA levels of MMP-2 and MMP-9 were decreased after treated with PFE in endometriosis cells. Besides, in vivo study, PFE treatment significantly inhibited the formation of endometriotic lesions in autologous transplanted mouse models of endometriosis. Kim et al summarized that PFE inhibited the adhesion and migration of endometriotic cells and suppressed the establishment of ectopic endometrial lesion tissue by downregulating MMP-2 and MMP-9 levels, and by regulating the ERK1/2 signaling pathway.⁸⁸

Saponin Extract

Korean red ginseng is commonly used in traditional oriental medicine, and it possesses various pharmacological activities such as anti-inflammatory,⁹⁰ autophagy-promoting,⁹¹ antioxidant,⁹² and antitumor⁹³ effects. Increasing evidence suggests that aberrant microRNA (miRNA) expression is associated with the pathogenesis of endometriosis.^{94–96} Cleaved caspase-3 is a traditional marker of activated cell death.^{97,98} Park's team demonstrated that saponin extract exposure dramatically decreased miR-21-5p expression in HESCs and upregulated caspase-3 expression, which in turn promoted cell apoptosis. HESCs transfected with miR-21-5p inhibitor could upregulate the expression of caspase-3 and could promote apoptosis in HESCs. They also analyzed that modulating the expression level of miRNA might be one of the molecular mechanisms by which saponin extract exerted its anti-endometriosis effect.⁹⁹

Zingiber Officinale Roscoe (Ginger) Extract

Zingiber officinale Roscoe (Ginger) is classified into the Zingiberaceae family and is a spice commonly used in the daily diet. Ginger is rich in several chemical constituents and shows various pharmacological properties, including anti-inflammatory, antibacterial, anticancer, and antioxidant properties.¹⁰⁰ The biological activities of ginger are mainly due to its phenols. Filho et al suggested that ginger extract reduced the volume of ectopic endometrial lesions in Wistar rats, a model of surgically induced endometriosis. However, the expression level of IL-6 and TNF- α in the peritoneal lavage fluid was not affected.¹⁰¹ This result contradicts the conclusion of Mao's team in their review that ginger extract has anti-inflammatory property.¹⁰⁰ The reason for the difference in results might be the short exposure time and the low dose of ginger extract used in their experiments.¹⁰¹

Extract of *Urtica Dioica* L

Urtica dioica L. is a perennial herb in the family Urticaceae.¹⁰² Ilhan et al found that flavonoids from *Urtica dioica* L. decreased the expression levels of TNF- α , VEGF, and IL-6 in the peritoneal fluid of Wistar albino rats endometriosis model, reduced the adhesion score of ectopic endometrial lesions and decreased the volume of ectopic lesions. They concluded that the anti-endometriosis effect of the methanolic extract of *Urtica dioica* L. was mainly attributed to its flavonoids.¹⁰³

Purified Bioactive Compounds

Apigenin

Apigenin (Figure 2) is isolated from vegetables and fruits, including bergamot, parsley and orange.¹⁰⁴ Apigenin has a wide range of biological properties, such as antitumor,¹⁰⁵ anti-inflammatory,¹⁰⁶ and pro-apoptotic¹⁰⁷ properties. Park et al demonstrated that apigenin could inhibit the proliferation and induce apoptosis of human endometriosis cells. Treatment of apigenin on vaginal mucosa-derived epithelial endometriotic cells (VK2/E6E7) and endocervix-derived endometriotic cells (End1/E6E7) cells resulted in the loss of mitochondrial membrane potential, increased calcium in the cytoplasm,

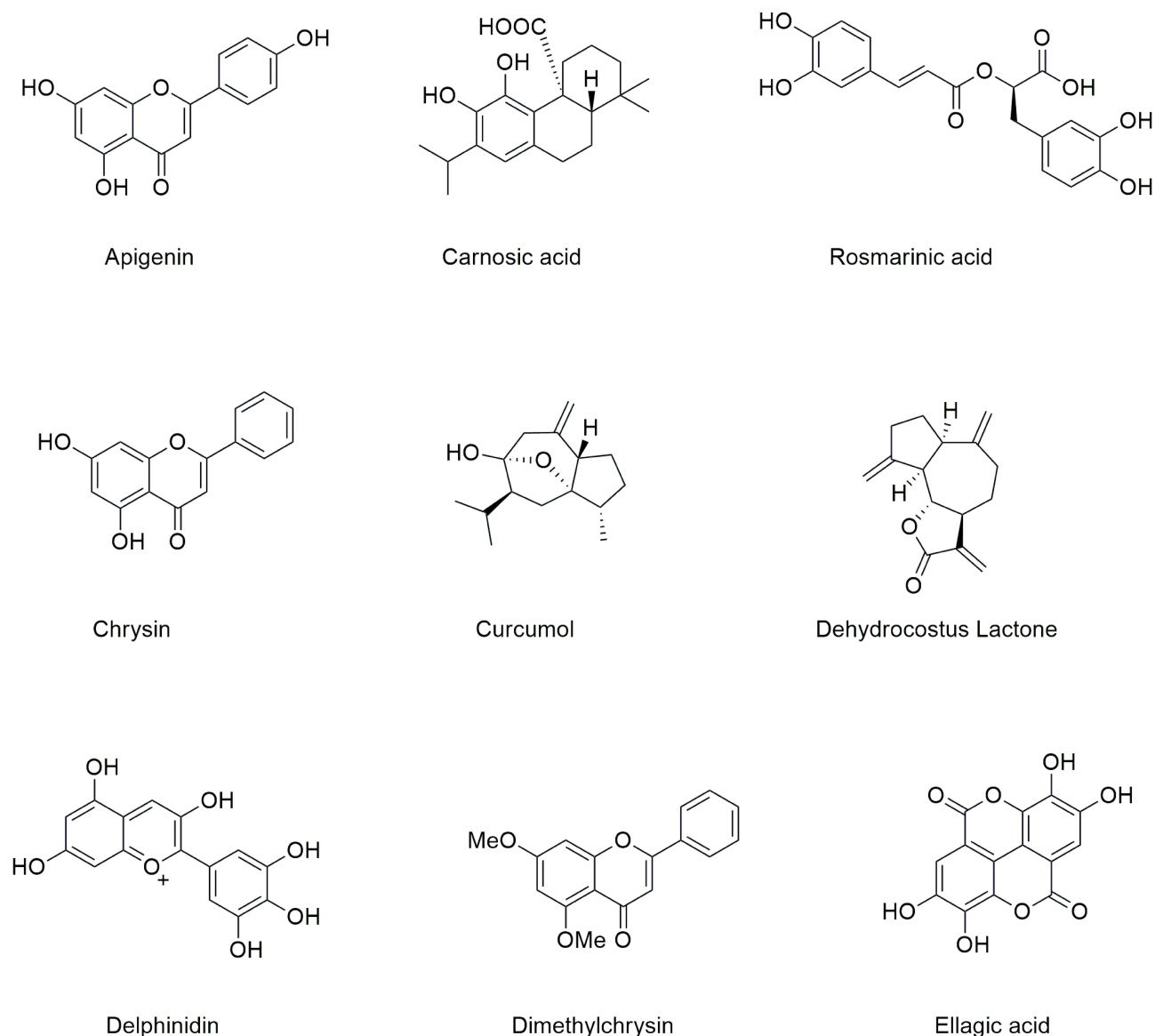


Figure 2 Structures of bioactive compounds (part 1) against endometriosis.

elevated the expression of the pro-apoptotic protein Bax, and the release of cytochrome c (Cyt c).¹⁰⁸ Released Cyt c and apoptotic protease activating factor-1 (Apaf-1) form a multimeric complex, then the caspase recruitment domain (CARD) at the amino terminus of Apaf-1 recruits the cytoplasmic caspase-9 precursor to form a new complex. This new complex activates downstream caspase-3 and caspase-7 to cause apoptosis (Figure 3).⁹⁷ In protein synthesis, the endoplasmic reticulum is also involved in the processing and transmission of apoptotic signals. Apigenin treatment increased the production of ROS and the expression of endoplasmic reticulum stress proteins in VK2/E6E7 and End1/E6E7 cells.¹⁰⁸ The protein kinase RNA-like ER kinase (PERK), eukaryotic translation initiation factor 2 α (eIF2 α), glucose regulatory protein (GRP78), and growth arrest and DNA damage 153 (GADD153/CHOP) are all endoplasmic reticulum stress-related proteins. In VK2/E6E7 and End1/E6E6 cells, the phosphorylation levels of PERK and eIF2 α were upregulated, and even GADD153 and total GRP78 proteins were increased after the treatment of apigenin.¹⁰⁸ When endoplasmic reticulum stress (ERS) is severe and persistent, it can trigger apoptosis by activating the endoplasmic reticulum (ER) pro-apoptotic cysteine protease caspase-12 and inhibiting the expression of Bcl-2.⁹⁸ Park et al also found that the pro-

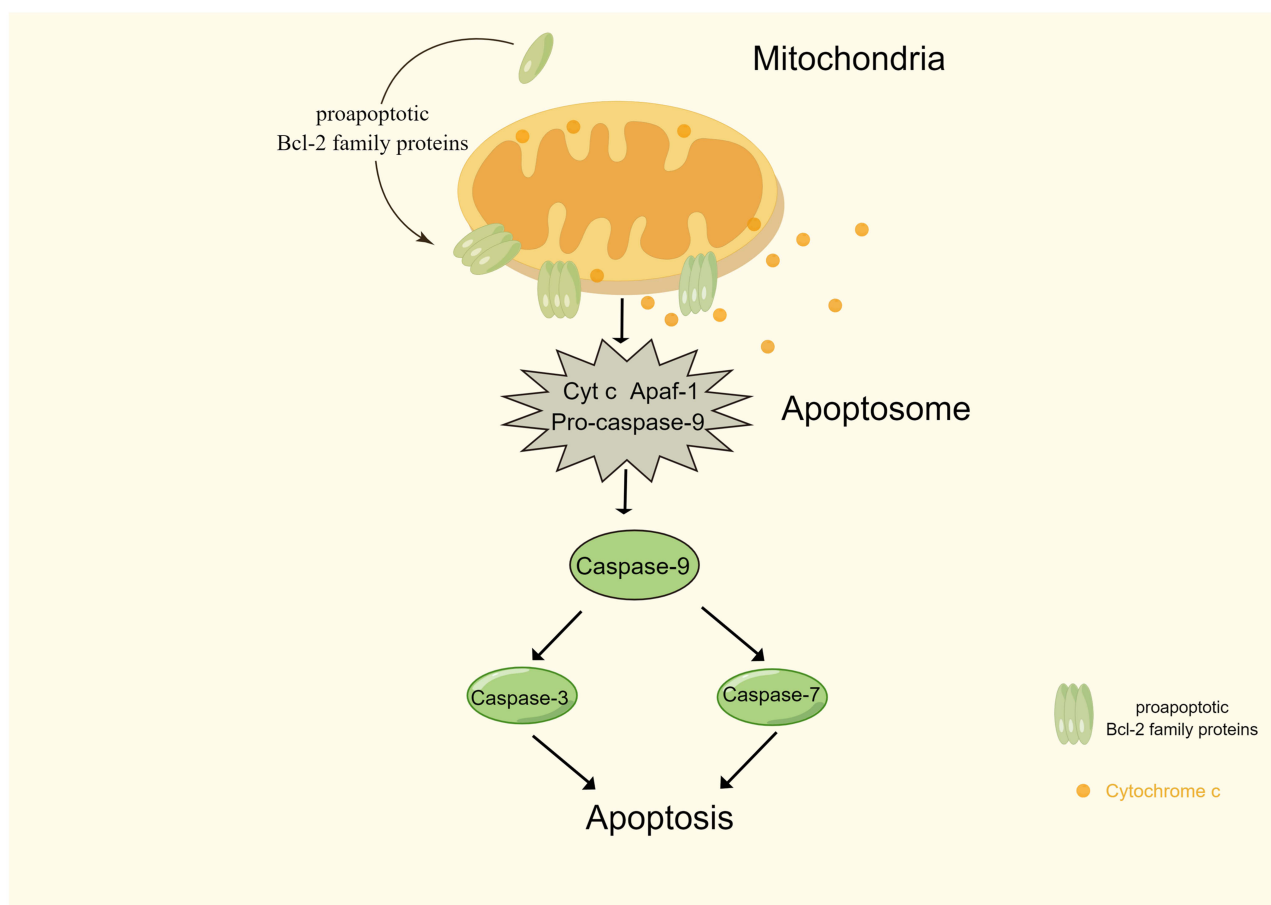


Figure 3 In the mitochondrial pathway, the death signal activates members of the Bcl-2 family, such as Bax. Bax can be inserted into mitochondrial membrane, causing changes in mitochondrial membrane permeability, and releasing Cyt c. Released Cyt c and Apaf-1 form a multimeric complex, then the CARD at the amino terminus of Apaf-1 recruits the cytoplasmic caspase-9 precursor to form a new complex. This new complex activates downstream caspase-3 and caspase-7 and finally cause apoptosis.

apoptotic effect of apigenin on endometriosis cells and the inhibitory effect on cell proliferation were achieved through modulating MAPK and PI3K/Akt signaling pathways.¹⁰⁸

Carnosic Acid and Rosmarinic Acid

The phenolic diterpene carnosic acid (CA, [Figure 2](#)) and the polyphenol rosmarinic acid (RA, [Figure 2](#)) are abundantly identified from rosemary (*Rosmarinus Officinalis*) leaves.^{109,110} Previous studies have demonstrated that this plant shows antioxidant,¹¹⁰ anti-inflammatory,¹¹¹ anti-cancer properties.¹¹² Ferella et al proposed that CA and RA could significantly inhibit the proliferation of Telomerase-immortalized human endometrial stromal cells (T-HESC) and primary endometrial stromal cells. CA induced cell cycle arrest at the G2/M phase, but CA had no effect on the change of intracellular reactive oxygen species (ROS) level. RA reduced intracellular ROS accumulation and exerted antioxidant properties. CA and RA significantly reduced the area of ectopic endometrial lesions in a mouse model of surgically induced endometriosis.¹¹³

Chrysin

Chrysin ([Figure 2](#)) is a flavonoid obtained from natural materials such as honey, propolis, flat mushrooms, and passion flowers.^{114,115} Chrysin has a variety of biological functions, including antiproliferative,¹¹⁶ anti-inflammatory,¹¹⁷ and antioxidant¹¹⁸ effects. Ryu et al showed that chrysin might exert anti-proliferative and pro-apoptotic effects on human endometriosis cells by regulating endoplasmic reticulum stress and the PI3K/Akt signaling pathways. They also found that chrysin varied the cell cycle ratio by increasing the proportion of End1/E6E7 cells and VK2/E6E7 cells in the sub-G1 phase and decreasing the proportion of cells in the G0/G1 phase. Cytoplasmic calcium levels, ROS, and a key protein

of endoplasmic reticulum stress GRP78, were significantly increased in chrysin-treated endometriosis cells.¹¹⁹ The endoplasmic reticulum is the main site of intracellular protein synthesis and a major reservoir of Ca^{2+} . Oxidative stress and disturbance of endoplasmic reticulum calcium metabolism may disrupt endoplasmic reticulum homeostasis, leading to endoplasmic reticulum stress, which then induces the unfolded protein response (UPR) to adapt to these changes. When ERS is severe and persistent, UPR eventually activates the expression of endoplasmic reticulum pro-apoptotic caspase-12. Activated caspase-12 can further shear caspase-3, eventually inducing apoptosis (Figure 4).⁹⁸

Curcumol

Curcumol (Figure 2) is a dominating constituent isolated from the root of the herbal plant turmeric.¹²⁰ Curcumol possesses significant pharmacological activities such as anti-cancer,¹²¹ anti-inflammatory,¹²² and anti-fibrotic.¹²³ Wang et al investigated that curcumol inhibited the progression of endometriosis by inhibiting the JAK2/STAT3 pathway in vivo and in vitro.¹²⁴ JAK2/STAT3 is an important signaling axis in the cell proliferation, apoptosis, and inflammation. Cytokines such as IL-6 and interferon can activate JAK2/STAT3 signaling pathway and phosphorylate STAT3. The phosphorylated STAT-STAT dimer enters the nucleus and then participates in the transcriptional regulation of related target genes, such as Bcl-2 and caspase-3, ultimately leading to the sustained proliferation of ectopic endometrium and enhanced resistance to apoptosis.^{124–126} Curcumol reduced the production of inflammatory cytokines such as TNF- α , IL-6, and IL-1 β of ectopic endometrial stromal cells (EESCs). This team also demonstrated that curcumol suppressed the proliferation of EESCs, accelerated cell apoptosis, and attenuated cell migration activity by MTT assay, wound healing assay, and flow cytometry. Curcumol also promoted the upregulation of apoptosis-related proteins Bax and caspase-3 and the downregulation of the expression of anti-apoptotic protein Bcl-2 in ectopic lesions in rats with autologous transplants of endometriosis. Curcumol also reduced the expression of TNF- α , IL-6, and IL-1 β in the peritoneal fluid of rats with endometriosis.¹²⁴

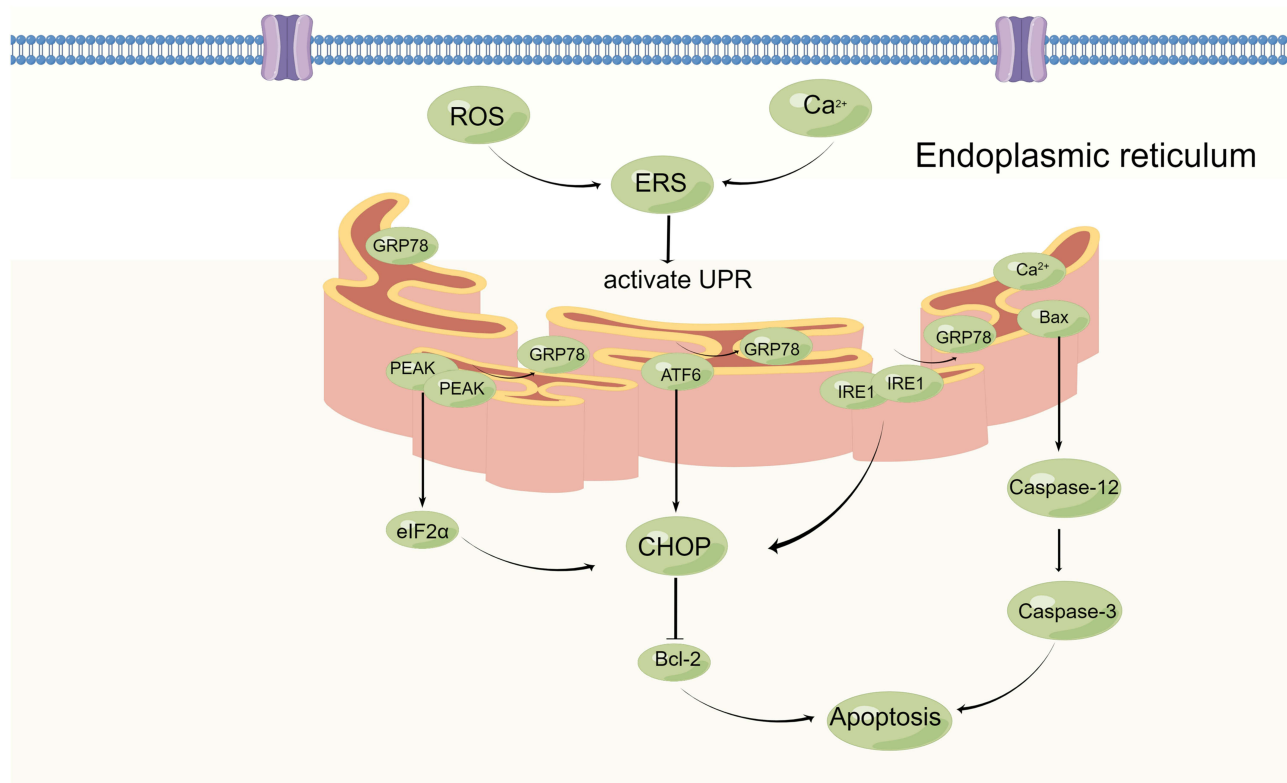


Figure 4 Oxidative stress and disturbance of endoplasmic reticulum calcium metabolism may disrupt endoplasmic reticulum homeostasis, leading to endoplasmic reticulum stress, which then induces the UPR to adapt to these changes. If UPR continue to accumulate in the ER, GRP78 can be released from IRE1, ATF6 and PERK. Furthermore, GRP78 binds to unfolded proteins to activate three signaling proteins, namely PERK, ATF6, and IRE1, which are responsible for ERs and signaling transmission. When ER stress is persistent and severe, it promotes cell apoptosis by upregulating the expression of GADD153/CHOP, by activating caspase-12, and by inhibiting Bcl-2 expression.

Daidzein-Rich Isoflavone Aglycones

Soy glycosides are isoflavone glycosides that are extracted from soybeans. However, they have high hydrophilicity and high molecular weight, which cannot be absorbed directly by the intestine. To be absorbed, they need to be degraded by the glucosidase in the intestinal flora. Soy glycosides are transformed into Daidzein-rich isoflavone aglycones (DRIsAs) after removal of the sugar chain, which can be absorbed rapidly and efficiently by the intestine.¹²⁷ NF- κ B dimers (p50 and p65) bind to I κ B to form a complex. This complex is retained in the cytosol at rest. IL-1 β stimulation causes activation of the I κ B kinases (IKKs) complex, then IKKs activation leads to I κ B ubiquitination and subsequent proteasomal degradation. This results in the release of the nuclear factor- κ B dimer (p50 and RelA/p65), which is translocated to the nucleus for regulation of transcription.^{128,129} Activation of the NF- κ B pathway contributes to the elevation of inflammatory cytokines, such as IL-6 and IL-8¹³⁰ (Figure 5). The results of Takaoka et al suggested that DRIsAs might exert anti-inflammatory and proliferation-inhibiting effects by inhibiting phosphorylation of I κ B and nuclear translocation of p65. In the endometriosis mouse model, DRIsAs-containing diets significantly reduced the percentage of Ki-67-positive cells in endometriotic lesions.¹³¹ Bulun's group proposed that estrogen stimulates the expression of cyclooxygenase-2 (COX-2) and the production of prostaglandin E2 (PGE2) through estrogen receptors (ERs). Then PGE2 can stimulate the expression of the aromatase gene in endometrial stromal cells. Ultimately, aromatase locally converts cholesterol to estradiol, thus forming a vicious cycle.² Takaoka et al stated that the expression of estrogen receptor β (ER β) in ovarian endometrial stromal cells (OESCs) was suppressed at the gene and protein levels after DRIsAs treatment, which in turn inhibited the expression of COX-2 and the production of PGE2. The decreased

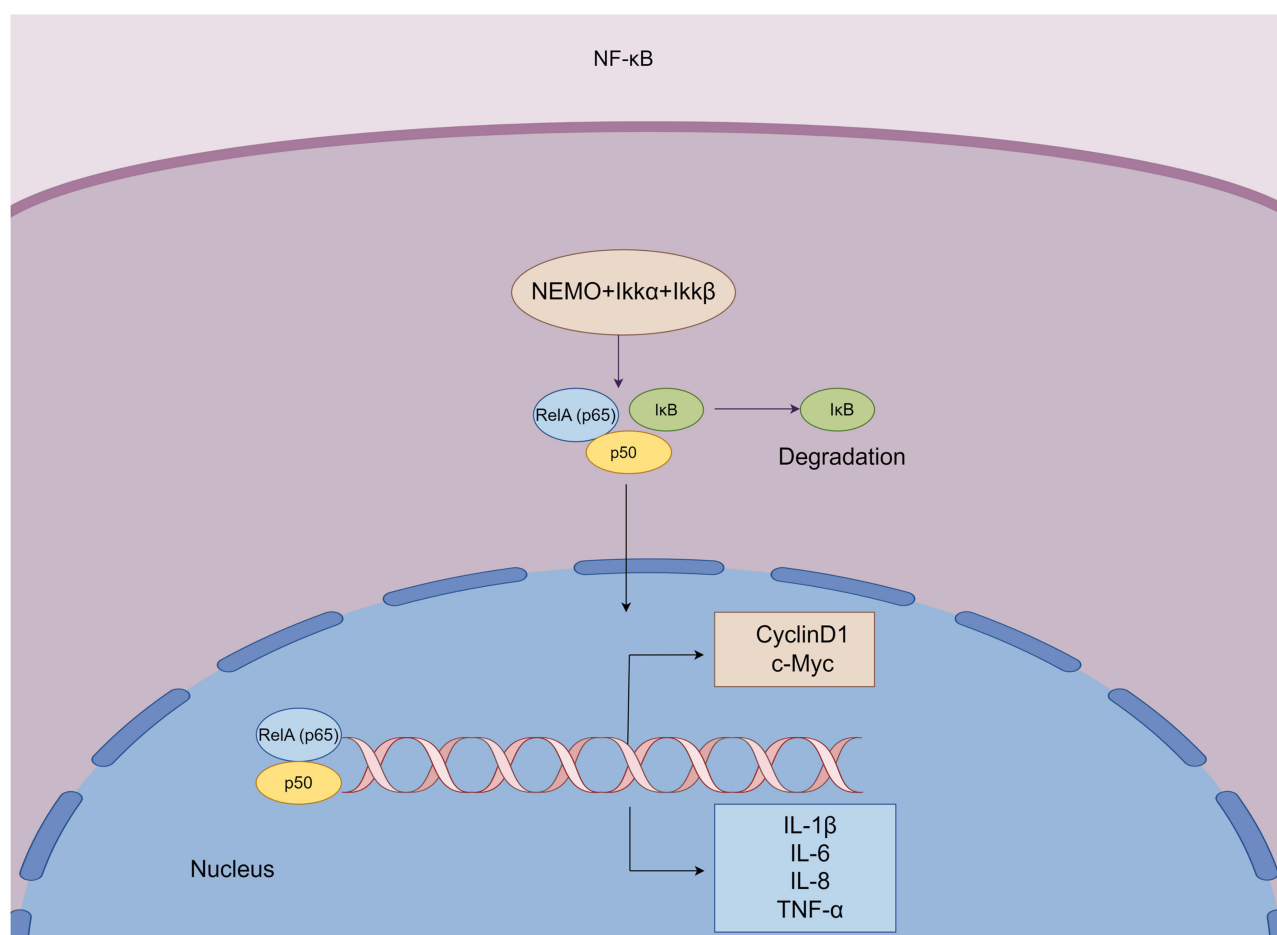


Figure 5 NF- κ B dimers (p50 and p65) bind to I κ B to form a complex. The activation of I κ B kinases (IKKs) complex leads to I κ B ubiquitination and subsequent proteasomal degradation. This results in the release of the nuclear factor- κ B dimer (p50 and RelA/p65), which is translocated to the nucleus for regulation of transcription. Activation of the NF- κ B pathway induces transcription of target genes, such as CyclinD1, c-Myc, IL-1 β , IL-6, TNF- α , etc.

expression of PGE2 results in the decrease of aromatase activity.¹³¹ In conclusion, because of the inhibition of ER β -mediated proliferative and anti-apoptotic effects in endometriosis stromal cells, DRAs are expected to be a new therapeutic candidate drug for endometriosis.

Dehydrocostus Lactone

Dehydrocostus lactone (DHL, [Figure 2](#)) is a natural sesquiterpene lactone, mainly extracted and purified from the root of the medicinal plant *Aucklandia lappa*.¹³² Dehydrocostus lactone exerts different pharmacological benefits, including pro-apoptotic,¹³³ anti-proliferative,¹³⁴ anti-fibrotic,¹³⁵ and anti-inflammatory.¹³⁵ It is well known that initiation of the caspase cascade is essential for cell apoptosis. Woo et al showed that DHL induced apoptosis of the human endometriotic 12Z cells by activating the caspase cascade.¹³⁶ PGE2 is a pivotal factor causing inflammation and pain allergy in patients with endometriosis.¹³⁷ COX-2 is the key enzyme for the biosynthesis of PGE2 by arachidonic acid.¹³⁸ DHL exposure significantly reduced the expression of PGE2 and COX-2 in 12Z cells.¹³⁶ Neurotrophins, known as endometriosis-related pain factors, are a family of nerve growth factors such as BDNF, NGF, NT-3, and NT-4/5, which are over-expressed in patients with endometriosis.⁸¹ Treatment with DHL significantly reduced the expression of NGF, NT-3, BDNF, and NT-4/5 in 12Z cells.¹³⁶ Previous studies have demonstrated an increase in M2 macrophages in lesions of patients with endometriosis.¹³⁹ Activated M2 macrophages promote tissue remodeling and angiogenic activity.¹⁴⁰ In the tumor microenvironment, M2 macrophages have been shown to induce angiogenesis, metastasis, and immune escape through the production of various factors such as VEGF, MMP-2, MMP-9 and IL-10.^{141,142} In contrast, monocyte chemoattractant protein-1 (MCP-1), as a chemokine, is responsible for the recruitment of macrophages to endometriotic lesions.¹⁴³ Huang et al found that alternate activation of macrophages (M2 polarization) was significantly inhibited after the treatment with dehydroxylactone. DHL stimulated the decreased expression of CD206 and TREM-2, as the markers of the endometriosis-associated macrophage M2 phenotype, as well as the decreased expression of MCP-1 and M2-related molecules (IL-10, VEGF, MMP-2 and MMP-9).¹³⁶ These effects of DHL might be achieved through inhibition of the Akt and NF- κ B pathways.¹³⁶

Delphinidin

Delphinidin ([Figure 2](#)) is originally isolated from brightly colored pigments of vegetables and fruits.¹⁴⁴ Delphinidin is an anthocyanin with anti-inflammatory, anti-angiogenic, antioxidant, and anti-cancer properties.^{144–146} Delphinidin exhibited anti-proliferative and pro-apoptotic effects in a dose-dependent manner on human endometriosis-derived cell lines by regulating the cell cycle according to the results of Park S. The immunofluorescence intensity of proliferating cell nuclear antigen (PCNA) was decreased after the treatment of delphinidin in both cell lines.¹⁴⁷ In addition, the decrease in mitochondrial membrane potential, the gradual increase in intracellular calcium ion levels, and cellular mitochondrial dysfunction occurred with the increasing doses of delphinidin treatment, ultimately led to endometrial cell apoptosis.¹⁴⁷ When the intracytoplasmic Ca²⁺ concentration increases, it can activate calcium-dependent proteases and the opening of transition pores, then affect mitochondrial permeability and result in the loss of mitochondrial membrane potential.^{97,148–150} When mitochondrial membrane potential begins to decline, mitochondria release cytochrome c into the cytoplasm. Cyt c and Apaf-1 are released to form a multimeric complex. CARD at the amino terminus of Apaf-1 recruits the cytoplasmic caspase-9 precursor to form a new complex. This new complex initiates the caspase cascade reaction and activates downstream caspase-3 and caspase-7, thereby inducing apoptosis.⁹⁷ Park et al showed that the antiproliferative effect of delphinidin was achieved through the regulation of the PI3K/Akt and MAPK signaling pathways.¹⁴⁷

Dimethylchrysin

Dimethylchrysin ([Figure 2](#)) is the totally methylated form of Chrysin. *Kaempferia parviflora* (*K. parviflora*, KP) are good sources of dimethylchrysin, which is extensively used in Thai and Lao folk medicine.^{151,152} Park et al observed that dimethylchrysin had anti-proliferative and apoptotic effects on VK2/E6E7 and End1/E6E7 cells.¹⁵² Treatment of dimethylchrysin in two endometriosis cell lines led to reduced cell proliferation by inactivating the PI3K/Akt pathway. Dimethylchrysin also accelerated cell apoptosis through DNA breakage and cell cycle arrest. In addition, dimethylchrysin could mediate mitochondrial and endoplasmic reticulum apoptotic pathways by inducing ROS production,

intracellular calcium ion dysregulation, and mitochondrial membrane potential loss in human endometriosis-derived cell lines.¹⁵² Oxidative stress and disturbance of endoplasmic reticulum calcium metabolism may disrupt ER homeostasis, then lead to the production of unfolded proteins in ER. If unfolded proteins continue to accumulate in the ER, GRP78 (also known as BIP) can be released from inositol-requiring kinase/endonuclease 1 (IRE1), activating transcription factor 6 (ATF6) and protein kinase activated by PERK. Furthermore, GRP78 binds to unfolded proteins to activate three signaling proteins, namely PERK, ATF6, and IRE1, which are responsible for ERs and signaling transmission. However, when ER stress is persistent and severe, UPR is insufficient to restore ER function, it promotes cell apoptosis by upregulating the expression of GADD153/CHOP, by activating caspase-12, and by inhibiting Bcl-2 expression.⁹⁸ Their study also demonstrated that the expression levels of GRP78 and IRE1 α were increased in a dose-dependent manner after the treatment of dimethylchrysin.¹⁵² Dimethylchrysin holds promise to inhibit the progression of endometriosis.

Ellagic Acid

Ellagic acid (EA, Figure 2) belongs to the group of polyphenol. EA can be found in various vegetables, fruits, and nutmeat.¹⁵³ It possesses a wide range of biological activities and has a variety of mechanisms of action. EA exhibits pro-apoptotic, anti-angiogenic, anti-proliferative, anti-inflammatory, antioxidant, anti-migration, and anti-invasion effects.^{154,155} Cell migration, attachment, proliferation, and invasion are closely related to the pathogenesis of endometriosis. And simultaneously they are involved in the onset, development, and growth of ectopic endometrial lesions.⁵³ Mc Cormack et al demonstrated that EA affected the cell cycle progression of T-HESCs by arresting the cell cycle in the G2/M phase. Besides, EA inhibited the migration and adhesion of endometrial epithelial cells (ECC-1) and T-HESCs. Taken together, EA can suppress the progression of endometriosis.¹⁵⁶

Epigallocatechin-3-Gallate

Epigallocatechin gallate (EGCG, Figure 6) is found with a high concentration in green tea, and exerting a wide range of pharmacological benefits. Kamal et al summarized in a review that EGCG had anti-angiogenic, anti-fibrotic, antiproliferative, antioxidant, and pro-apoptotic effects.¹⁵⁷ E-cadherin mediates abnormal cell adhesion function. Reduced expression of E-cadherin can loosen cell adhesion, facilitate cell movement, and accelerate cell metastasis and

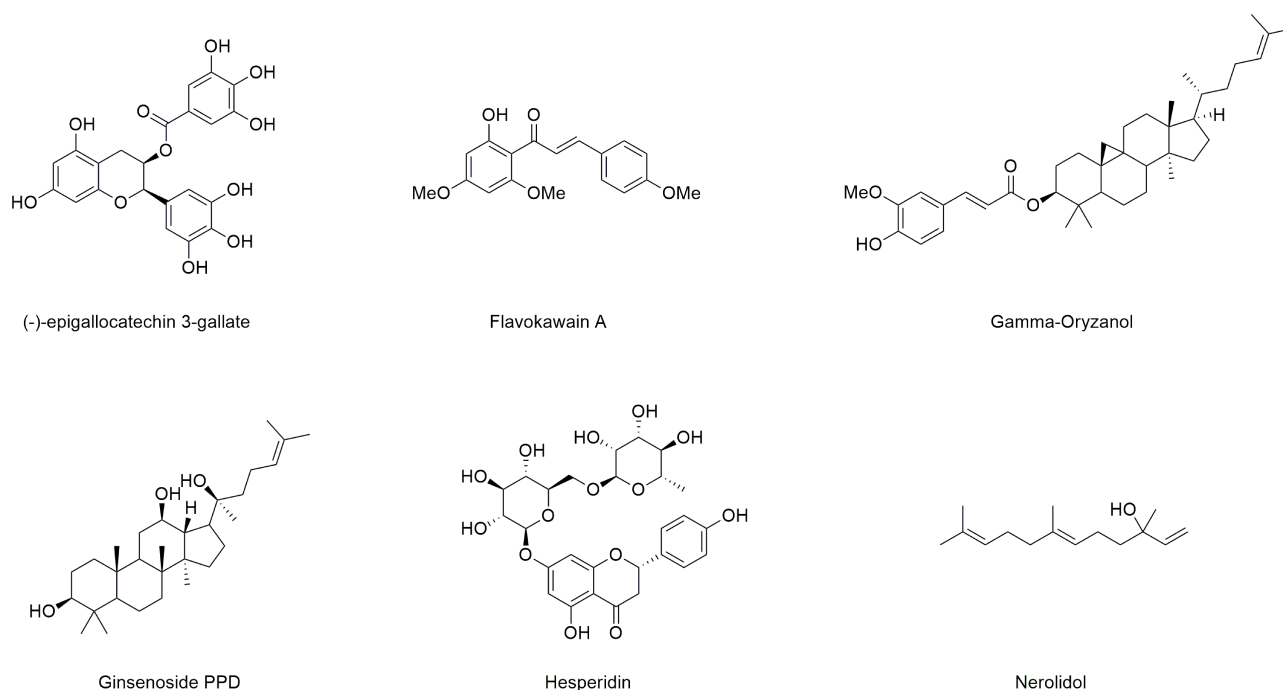


Figure 6 Structures of bioactive compounds (part 2) against endometriosis.

invasion.¹⁵⁸ Guan et al showed that EGCG was effective in inhibiting the progression of endometriosis. EGCG reduced the size of the ectopic endometrium in an endometriosis nude mouse model. Guan proposed the mechanism of the anti-endometriosis effect of EGCG was the demethylation of the E-cadherin promoter region, resulting in the upregulation of E-cadherin expression.¹⁵⁹

Flavokawain a

Kava-kava, known as the piper methysticum, is a medicinal plant belonging to the pepper family. Flavokawain A (FK A, Figure 6) is a chalcone isolated from kava-kava.¹⁶⁰ Flavokawains mainly have anti-cancer¹⁶¹ and anti-inflammatory¹⁶² biological activities. Wei et al established a rat model of endometriosis by autologous transplantation. After the treatment of FK A, the inflammatory cytokines in peritoneal fluid and plasma, such as IL-1 β , IL-8, nitric oxide (NO), COX-2, and PGE2 were decreased. In addition, FK A could promote the expression of apoptosis-related proteins Bax and cleaved caspase-3, and also reduce the expression of anti-apoptotic protein Bcl-2 in ectopic endometrial tissues. The expression of VEGF in peritoneal fluid and plasma of rats treated with FK A was decreased too. The authors proposed that FK A can exert anti-inflammatory, pro-apoptotic, and anti-angiogenic effects by inhibiting the overactivation of PI3K/Akt and NF- κ B signaling pathways, ultimately inhibiting the progression of endometriosis.¹⁶³

Gamma Oryzanol

Gamma oryzanol (GO, Figure 6) is mainly found in rice bran and rice bran oil.^{164,165} Gamma oryzanol has abundant biological activities, including antioxidant^{165,166} and anti-inflammatory.¹⁶⁷ Eisalou et al demonstrated that GO decreased steroidogenic factor 1 (SF1) expression and upregulated BECN1 expression in autologous transplanted rat endometriotic lesions.¹⁶⁸ SF1, also known as NR5A1, is an orphan nuclear receptor, and there is no clear natural ligand for SF1. SF1 plays a key role in regulating the steroid synthesis pathway in the ovary. SF1 can bind to the promoters of several steroidogenic genes, such as steroid synthesis acute regulatory protein (STAR) and aromatase, which can result in the production of high amounts of estradiol.² It is well known that increased estradiol synthesis promotes the proliferation of endometriotic lesions, inhibits cell apoptosis, and promotes the occurrence and development of endometriosis. Beclin1 is a specific marker of autophagy.^{169,170} In conclusion, GO may inhibit the progression of endometriosis by decreasing estrogen production and increasing cell autophagy.

Ginsenoside PPD

Ginseng is a traditional herbal medicine, while ginsenosides PPD (Figure 6) is the dominating bioactive component of the Panax genus.¹⁷¹ Ginsenoside PPD has significant biological activity, such as anti-inflammatory¹⁷² and anti-cancer.¹⁷³ There are strong evidences that estrogen dependence, progesterone resistance, and immune system defects, play important roles in the development of endometriosis.^{2,53} Cellular autophagy is another type of programmed cell death. Under the influence of external environmental factors, cells use lysosomes to degrade their own damaged, degenerated, or senescent macromolecules as well as organelles (such as mitochondria, and endoplasmic reticulum). Autophagy is a self-protective mechanism and plays a vital role in regulating cell survival and death.¹⁷⁴ Mei et al found that estrogen could inhibit autophagy in endometrial stromal cells (ESCs) by up-regulating the expression of chemokine CXCL12 and CXCR4 (the receptor of CXCL12).¹⁷⁵ Zhang et al believed that increased expression of estrogen and estrogen receptor α (ER α) inhibited autophagy and apoptosis in EESCs, however, PPD could reverse this inhibition. PPD treatment significantly downregulated the expression of ER α and upregulated the expression of progesterone receptor (PR). Subsequently, PPD induced a high level of autophagy in EESCs, upregulated the expression of pro-apoptotic molecules, Bax/Bcl-2 antagonist/killer (Bak), and downregulated the expression of anti-apoptotic molecules (Bcl-2/Bcl-xL). What's more, progesterone can prevent the inhibitory effect of estrogen on autophagy in EESCs. PPD could decrease the expression of ER α and increase the expression of PR α in ectopic lesions in a mice model of endometriosis, then lead to autophagy. In addition, PPD could upregulate granzyme B and perforin, activating natural killer (NK) cells. The activated NK cells exerted cytotoxic effects on EESCs, enhanced the immune surveillance of ectopic lesions, and inhibited the progression of endometriotic lesions.¹⁷⁶

Hesperidin and Nerolidol

Hesperidin (Figure 6) is a bioflavonoid that is abundant in citrus fruits, including lemons, oranges and grapefruits.^{177,178} Nerolidol (Figure 6) exists in the essential oils of many plants with a floral aroma.^{179,180} Hesperidin and nerolidol have a variety of physiological actions, including anti-inflammatory effects, antioxidant, and other effects.^{177,179–181} Like vitamin C, hesperidin exerts its anti-inflammatory effect by inhibiting the NF- κ B signaling pathway and reducing inflammatory cytokines, such as TNF- α , IL-6, and IL-1 β .¹⁸² Nerolidol also exerts anti-inflammatory properties by reducing the levels of TNF- α and IL-1 β , as well as by reducing the number of polymorphonuclear cells.¹⁸³ Treatment with hesperidin or nerolidol resulted in obvious regression of surgically induced endometriosis foci in rats. Hesperidin or nerolidol treatment resulted in an obvious decrease in malondialdehyde (oxidant) levels, a significant increase in glutathione levels, and superoxide dismutase (antioxidant enzyme) activity. Hesperidin or nerolidol also improved the pathological status of inflammatory cell infiltration, tissue necrosis and hemorrhage, and vascular congestion in endometriotic lesions in a rat model of endometriosis.¹⁸⁴ Since inflammation and oxidative stress have been considered as underlying factors in the pathophysiological mechanisms of endometriosis, hesperidin or nerolidol may provide a new strategy for the prevention and treatment of inflammatory diseases such as endometriosis.

Isoliquiritigenin

Isoliquiritigenin (ISL, Figure 7) is a natural chalcone isolated from the roots of *Glycyrrhiza* spp.¹⁸⁵ Previous studies showed the antioxidant,¹⁸⁶ anti-inflammatory,¹⁸⁷ anti-fibrosis,¹⁸⁸ and anticancer¹⁸⁹ effects of ISL. Epithelial mesenchymal transition (EMT) refers to the morphological transformation of epithelial cells into a fibroblastic or mesenchymal cell phenotype, with loss of cell polarity, cytoskeletal rearrangement, and increased migratory motility. The expression level of E-cadherin is negatively correlated with the invasive and metastatic ability of cells.^{158,190} Since E-cadherin has a stronger adhesive ability than N-cadherin, a decrease in E-cadherin expression and an increase in N-cadherin expression on the cell membrane surface increase cell motility and the ability to invade and metastasize.¹⁹¹ Snail and Slug can competitively bind to the E-box sequence of the proximal promoter of E-cadherin gene with SMAD-associated protein 1 (SIP1), thereby inhibiting the expression of E-cadherin and inducing EMT in cells.¹⁵⁸ Hsu et al found that the expression of E-cadherin was upregulated, however N-cadherin, Slug, and Snail could be reduced after isoliquiritigenin treatment, then inhibited EMT of End1/E6E7 and ectopic endothelial cells, thereby inhibiting migration of cells in vitro and in vivo. They also demonstrated that Bcl-2 and estrogen receptor β were decreased, while pro-apoptotic protein Bax and cleaved caspase-3 were upregulated in vivo. The expressions of IL-1 β , IL-6, and VEGF in serum and ectopic endometrial tissues were decreased after ISL treatment.¹⁹²

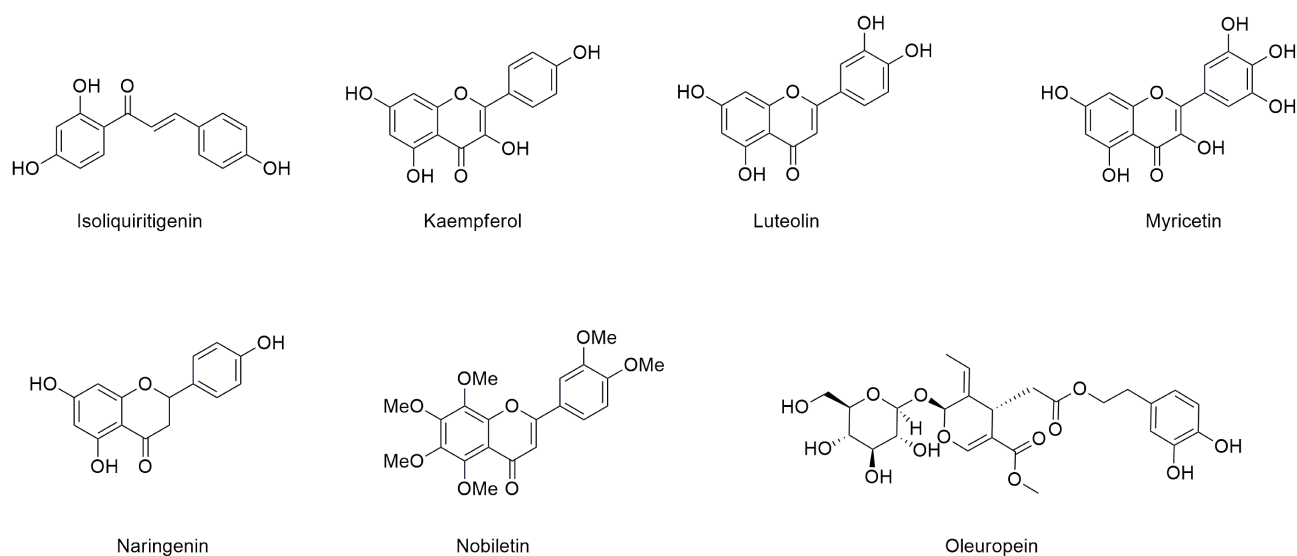


Figure 7 Structures of bioactive compounds (part 3) against endometriosis.

Kaempferol

Kaempferol (KP, [Figure 7](#)) is a dietary flavonoid mainly found in tea, some medicinal plants, fruits and vegetables.¹⁹³ Previous studies showed that kaempferol has anti-inflammatory,¹⁹⁴ anticancer,¹⁹⁵ and anti-angiogenic¹⁹⁶ biological properties. Presented by Zhao et al, the protein expression of PTEN was upregulated, while the expression level of MMP-9 was decreased in Ishikawa cells treated with kaempferol.¹⁹⁷ In the PI3K/Akt signaling pathway, PTEN can convert phosphatidylinositol 3,4,5-triphosphate (PIP3) to phosphatidylinositol 4,5-bisphosphate (PIP2), thereby preventing the phosphorylation of Akt, and then inhibiting the activation of PI3K/Akt/mTOR signaling pathway ([Figure 8](#)).¹⁹⁸ They also demonstrated that kaempferol exposure to Ishikawa cells inhibited cell migration and invasion by using scratch assay (wound healing) and perforation assay.¹⁹⁷

Luteolin

Luteolin ([Figure 7](#)) is a naturally occurring flavonoid that is widely distributed in flowers, vegetables, herbs, and spices.^{199,200} Cyclin D1 (CCND1), cyclin E1 (CCNE1), cyclin-dependent kinase 2 (CDK2), and cyclin-dependent kinase 4 (CDK4) are all cell cycle regulation-related proteins/genes, while CCND1 and CCNE1 are key molecules for G1 phase progression.^{201,202} Cyclin D1 can bind to either CDK4 or CDK6. Cyclin D1 overexpression allows cells to rapidly pass the G1/S checkpoint, resulting in a shortened S phase. In contrast, blocking or knocking down Cyclin D1 blocks the cell cycle and induces apoptosis. Cyclin E1 is the rate-limiting factor for the transition between G1 and S phases. Cyclin binds to the corresponding CDK to form a complex that promotes Rb protein phosphorylation, then the phosphorylated Rb releases the nuclear transcription factor E2F, which is free to enter the nucleus and promotes the transcriptional expression of downstream genes, allowing cells to move from G1 phase to S phase.^{203–205} The anti-proliferative and pro-apoptotic effects of luteolin on endometriosis have been demonstrated by Park et al in vivo and in vitro. Treatment with luteolin, VK2/E6E7 and End1/E6E7 cells were arrested in the sub-G0/G1 phase. Luteolin decreased the mRNA expression of CCNE1, CDK2, and CDK4, which in turn inhibited cell proliferation by preventing cell cycle progression.²⁰⁶ Activation of the pro-apoptotic proteins recombinant Bak and Bax can insert into the mitochondrial membrane, causing changes in mitochondrial membrane permeability, loss of transmembrane potential, then releasing of Cyt c. Cyt c can form a multimeric complex with Apaf-1, which can recruit the cytoplasmic

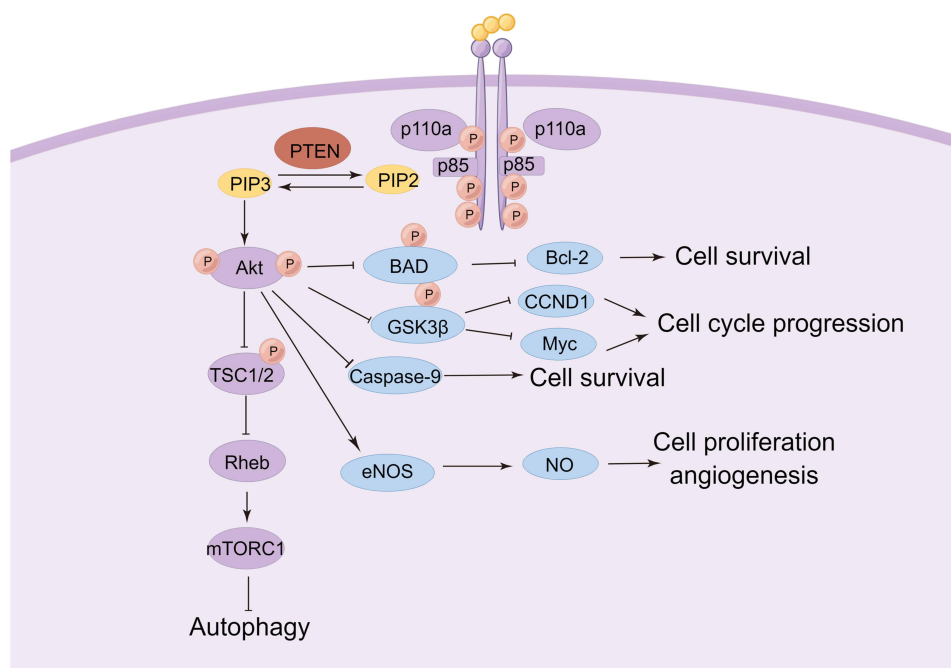


Figure 8 PI3K produces the second messenger PIP3 in cells, which then activates Akt. The activated Akt can inhibit the TSC1/2 complex, thus activating mTORC1 and inhibiting autophagy. In the PI3K/Akt signaling pathway, PTEN converts PIP3 to PIP2, thereby inhibiting Akt phosphorylation. Furthermore, the activation of PI3K/Akt/mTOR signaling pathway is inhibited. Caspase-9, Myc, CCND1, Bcl-2 and NO are downstream target genes of the PI3K/Akt/mTOR signaling pathway.

caspase-9 precursor through the CARD at the amino terminus of Apaf-1 to form a complex. This complex initiates the caspase cascade reaction, which activates downstream caspase-3 and caspase-7 to cause cell apoptosis.^{97,207} The endoplasmic reticulum is the main site of intracellular protein synthesis and a major reservoir of Ca^{2+} . Within the endoplasmic reticulum, disruption of calcium homeostasis or excessive accumulation of endoplasmic reticulum proteins induces caspase-12 expression on the endoplasmic reticulum membrane. Activated caspase-12 further shears caspase-3 and triggers apoptosis.⁹⁸ There is a correlation between the endoplasmic reticulum and the mitochondrial apoptotic pathway. When the intracytoplasmic Ca^{2+} concentration is elevated, it can activate calcium-dependent proteases, and affect mitochondrial permeability as well as membrane potential, thereby promoting apoptosis.^{97,148} Park et al illustrated that luteolin could also lead to cell apoptosis by causing intracellular calcium and ROS accumulation, by activating the pro-apoptotic proteins Bax and Bak.²⁰⁶ They suggested that these effects of luteolin were mediated through the regulation of PI3K/AKT and MAPK signaling pathways.²⁰⁶

Myricetin

Myricetin (MYR, Figure 7) belongs to flavonol, and commonly presents in fruits, vegetables, wines, berries and teas. Myricetin has a variety of pharmacological activities, including anti-inflammatory, anticancer, anti-angiogenesis, and anti-proliferation.^{208,209} Park et al showed that myricetin had anti-proliferative and pro-apoptotic effects in endometriosis.²¹⁰ Myricetin inhibited cell proliferation by reducing CCNE1 expression according to the results of Park et al. They also suggested that myricetin could inhibit the expression of Bcl-2 and induce the expression of Bax by regulating the MAPK signaling pathway. Moreover, myricetin induced apoptosis of endometriosis patient-derived cells (VK2/E6E7 and End1/E6E7) by mediating ROS, calcium ion accumulation, and causing changes in mitochondrial membrane potential (MMP).²¹⁰

Naringenin and Naringin

Naringenin (NGN, Figure 7) is a flavonoid compound, it is the aglycone of naringin. Naringenin can be found in citrus fruits (grapefruit, oranges) and tomatoes. Naringenin has a variety of biological activities.²¹¹ Nrf2 regulates the transcription of endogenous antioxidant enzymes, such as glutamate cysteine ligase (GCL) and glutathione (GSH). Furthermore, Nrf2 can protect against oxidative damage caused by oxidative stress and inflammation.²¹² Under basal conditions, Keap1 forms a complex with Nrf2, leading to ubiquitination and subsequent degradation of Nrf2. Under conditions of oxidative stress, Keap1-CUL3-E3 ubiquitin ligase undergoes conformational changes that disrupt the binding of Nrf2 to Keap1. Free Nrf2 translocates to the nucleus and transcribes antioxidant enzyme (NQO1, HO-1) genes.⁶⁵ Nrf2 and its downstream molecules (NQO1, HO-1) were significantly elevated in endometriotic lesions, and these antioxidants mitigated cell death by scavenging ROS (O_2^- and $\cdot\text{OH}$).²¹³ Kapoor et al illustrated that naringin treatment on endometrial cells significantly inhibited the expression of the Nrf2 protein and its downstream HO-1 and NQO1. In other words, a decrease in antioxidant enzymes means an increase in ROS. ROS can disrupt protein, lipid, and DNA structures, ultimately leading to cell apoptosis.^{213,214} The accumulation of ROS in the cell leads to unfolded protein response and induces endoplasmic reticulum stress. Kapoor et al demonstrated that naringenin significantly increased the loss of mitochondrial membrane potential and shifted the MMP toward depolarization. They also showed that naringenin decreased the expression levels of TNF- α , NO, MMP-2, and MMP-9. Naringin could accelerate mitochondria-mediated cells apoptosis by generating mitochondrial membrane potential depolarization, by increasing the expression level of Bax, by releasing Cyt c and activating caspase-3 in VK2/E6E7 and End1/E6E7 cells.²¹⁵ Taking together, naringin promoted apoptosis by inducing mitochondrial membrane depolarization, endoplasmic reticulum stress, ROS production, and regulating MAPK and PI3K/Akt pathways. In addition, naringin also exhibited anti-inflammatory and anti-invasive effects. These results suggest that naringenin can delay the progression and development of endometriosis.

Nobiletin

Nobiletin (Figure 7), a polymethoxyflavonoid isolated from citrus peel,²¹⁶ has a wide range of biological effects and plays an interesting role in anticancer,²¹⁷ anti-inflammatory,²¹⁸ and anti-oxidation.²¹⁹ Activation of the NF- κ B pathway induces transcription of target genes, such as Cyclin D1, c-Myc, IL-1 β , IL-6, TNF- α , etc.^{128,129,220,221} Wei et al found that nobiletin significantly reduced the gene expression levels of IL-6, IL-1 β , TNF- α , matrix metalloproteinase-1 (MMP-

1), and matrix metalloproteinase-3 (MMP-3). Compared with untreated endometriosis mice, the expression levels of PCNA and VEGF were significantly reduced, however, E-cadherin was significantly increased in the nobiletin-treated group. The effects of nobiletin on endometriosis might be attributed to the inhibition of the activity of IKKs.²²²

Oleuropein

Oleuropein (Figure 7) is a polyphenolic compound extracted from olive.²²³ ER β can increase the proliferation of ectopic endometrial lesions and prevent apoptosis, thus promoting the progression of endometriosis.² Park et al found that oleuropein could selectively inhibit the activity of ER β , but had no effect on the activity of ER α . In addition, oleuropein reduced the expression of proliferation-related indicator Ki-67, promoted the expression of cleaved caspase-3 and reduced the expression of cellular inflammatory factors, thus the endometriosis was alleviated.²²⁴

Quercetin

Quercetin (Figure 9) is a polyphenolic flavonoid compound chemically.²²⁵ Quercetin is abundantly identified from fruits and vegetables, taking cilantro, grapes, apples, onions, and cherries as examples.^{226,227} The upregulation of CCND1 is tightly associated with the pathogenesis of endometriosis.²²⁸ CCND1 is the G1/S checkpoint of the cell cycle, and reduced expression of CCND1 is associated with G1 phase arrest.²²⁹ Park et al observed that quercetin induced cell cycle arrest in the G0/G1 phase by decreasing the expression of CCND1 protein and mRNA level, which in turn inhibited the proliferation of VK2/E6E7 and End1/E6E7 cells. Quercetin also induced apoptosis through the accumulation of ROS and the loss of mitochondrial membrane potential. Park et al suggested that the anti-proliferative and pro-apoptotic effects of quercetin might be achieved through regulation of MAPK and PI3K/Akt signaling pathway transduction.⁶ Jamali et al showed that the combined application of quercetin and metformin exerted anti-inflammatory effects by decreasing the inflammatory cytokine TNF- α .²³⁰ Increased expression of antioxidant enzymes can attenuate the oxidative stress response.²¹³ Quercetin could promote the expression levels of the Nrf2 gene and enhance the activity of its downstream target gene/antioxidant enzyme (NQO1).²³⁰ Kim et al demonstrated that mTOR played a negative regulatory role in the autophagy pathway.²³¹ In a surgically induced endometriosis model, the expression of the mTOR gene was reduced in ectopic endometriotic lesion tissues, and gene expression levels of autophagy markers (Beclin 1 and ATG5) were significantly increased.²³⁰

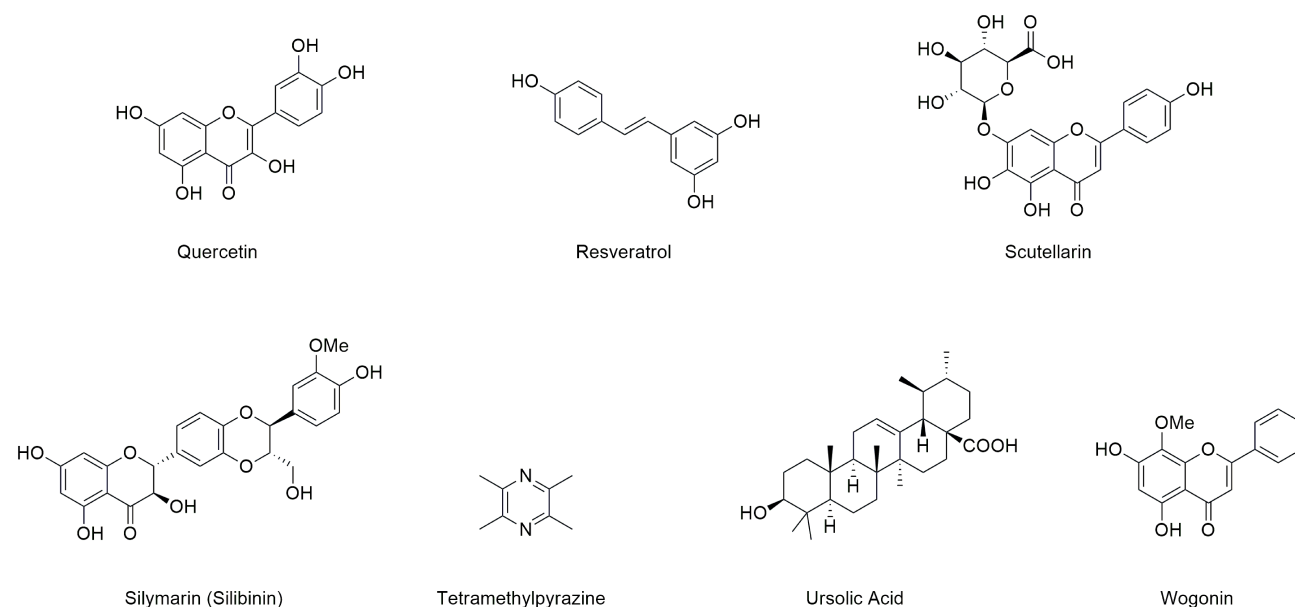


Figure 9 Structures of bioactive compounds (part 4) against endometriosis.

Resveratrol

Resveratrol (Figure 9) is a naturally occurring polyphenolic compound which is extensively present in grapes, red wine, and peanuts.²³² Resveratrol possesses pro-apoptotic,²³³ anti-angiogenic,²³⁴ anti-inflammatory,²³⁵ antioxidant²³⁶ and anti-tumor²³⁷ biological properties. Cell migration is associated with the aggressiveness of endometriosis,²³⁸ which depends on the ratio of matrix metalloproteinase (MMP)/TIMP1 (tissue inhibitor of metalloproteinase-1). Khodarahmian et al summarized that resveratrol could reduce the expression of VEGF, TNF- α protein, and mRNA levels in the eutopic endometrium of patients with endometriosis.²³⁹ Madanes et al illustrated that resveratrol could promote apoptosis by increasing the expression level of cleaved caspase-3, and could exert an anti-angiogenic effect by reducing the expression of VEGF and angiotensin converting enzyme-1 in 12Z and ST-T1b cells. Madanes et al also demonstrated that resveratrol treatment could exert an anti-invasive effect by decreasing the MMP-2/TIMP1 ratio in primary endometriotic stromal cells, 12Z and ST-T1b cells. Resveratrol could suppress cell migration.²⁴⁰ In conclusion, resveratrol reduces angiogenesis, migration, invasion, and inflammatory response in vitro and in vivo.

Scutellarin

Scutellarin (Figure 9) is classified as a flavonoid obtained from the medicinal plant *Erigeron breviscapus* (Vant). Hand-Mazz.²⁴¹ Scutellarin has been shown to have a variety of pharmacological effects, including anticancer, antioxidant, anti-proliferative, anti-invasive, anti-angiogenic, and anti-inflammatory effects.^{242–247} Like the eutopic endometrium, the ectopic endometrium also undergoes periodic bleeding and shedding under the regulation of estrogen, resulting in tissue damage. Platelets are involved in the repair of damaged tissue. Once tissue injury or trauma occurs, platelets are the first to reach the trauma site, initiating hemostasis, inflammation, and cell proliferation. In addition, they participate in the repair process of tissue remodeling. Activated platelets secrete a large number of bioactive molecules, including various cytokines and growth factors, such as VEGF, epidermal growth factor (EGF), TGF- β , and platelet-derived growth factor (PDGF).²⁴⁸ TGF- β induces the TGF- β /Smad signaling pathway, which is a critical pathway for regulating EMT. Activated platelets also drive transdifferentiation of fibroblasts to myofibroblasts (FMT) and smooth muscle metaplasia (SMM).²⁴⁹ Ding et al found that scutellarin could effectively restrain the development and progression of endometriosis by inhibiting the aggregation and activation of platelets, by inhibiting tissue proliferation, angiogenesis, and fibrosis.²⁵⁰

Silibinin

Silibinin (Figure 9) is isolated from the *Silybum marianum* (milk thistle) plant.^{251,252} Silibinin has numerous biological activities, principally such as antioxidant,²⁵³ anti-migration,²⁵⁴ anticancer²⁵⁵ and anti-inflammatory²⁵⁶ effects. Mirzaei's group divided 70 patients with endometriosis into an experimental group (silymarin group) and a control group (placebo group). Their results showed that silymarin decreased IL-6 expression of serum and reduced the size of endometriotic lesions.²⁵⁷ Ham et al demonstrated that silibinin exhibited anti-inflammatory, anti-proliferative, and pro-apoptotic effects in vitro and in vivo. The mRNA levels of TNF- α , IL-1 β , and IL-6 in ectopic endometriotic lesions were decreased after intraperitoneal injection of silibinin in a mouse model of endometriosis. Increased cytoplasmic calcium ion concentration, disrupted mitochondrial membrane potential, and increased oxidative stress after the treatment of silibinin in VK2/E6E7 and End1/E6E7 cells were observed.²⁵⁸ Oxidative stress, and disturbance of endoplasmic reticulum calcium metabolism may lead to elevated expression of endoplasmic reticulum stress-related proteins such as IRE1, ATF6, and PERK, which are responsible for ERS and signal transmission. When ERS is severe and persistent, the expression of GADD153/CHOP and caspase-12 can be upregulated, ultimately inducing apoptosis.⁹⁸ According to the results of Ham et al, silibinin could elevate the expression levels of both IRE1 α and PERK in human endometriosis-derived cells. Meanwhile, their downstream molecules, such as eIF2 α and GADD153/CHOP, were also elevated, ultimately resulted in apoptosis. Additionally, they suggested that silibinin could inhibit the proliferation of human endometriosis cells by regulating the MAPK signaling pathway.²⁵⁸

Tetramethylpyrazine

Tetramethylpyrazine (TMP, Figure 9), also known as ligustrazine, is a compound originally isolated from the Chinese herbal medicine chuanxiong.²⁵⁹ TMP exerts the effects of inhibition of platelet aggregation,²⁶⁰ antitumor,²⁶¹ anti-angiogenesis,²⁶² antioxidant,²⁶³ and anti-inflammation.²⁵⁹ Previous studies have shown that activated platelets contribute to EMT and FMT in endometriosis cells.²⁴⁹ E-cadherin is a marker for epithelial-like cells, while vimentin and α -smooth muscle actin (α -SMA) are markers for mesenchymal-like cells.^{158,264} Activated platelets can release TGF- β , which is associated with fibrosis.^{248,265} TGF- β can activate the expression of EMT-related transcription factors through the TGF- β /Smad signaling pathway, which in turn promotes cell invasion and metastasis.²⁴⁹ Type I collagen (Col-I) is a marker of collagen fibers. And α -SMA is a marker of smooth muscle cells and myofibroblasts, which are the important effector cells in the process of fiber formation. Fibroblasts can transform into myofibroblasts under the stimulation of TGF- β . Myofibroblasts can upregulate the expression of α -SMA and stimulate the production of Col-I, which in turn drives cell contraction and collagen production, ultimately promoting tissue fibrosis.^{266,267} TMP treatment increased the E-cadherin expression in a dose dependent manner. TMP could significantly inhibit the aggregation of platelets, the expression of TGF- β , α -SMA, and Col-I in vivo. Meanwhile, the weight of ectopic endometrial lesions and the degree of fibrosis were reduced in endometriosis mouse models. Taken these results together, TMP can slow the progression of endometriosis and fibrosis by inhibiting platelet activation, platelet-induced TGF- β , EMT, FMT, cell contraction, and collagen production.²⁶⁸

Ursolic Acid

Ursolic acid (UA, Figure 9) is a pentacyclic triterpenoid purified from medicinal plants. It is also extensively present in various fruits and vegetables.²⁶⁹ UA has several pharmacological activities, principally including antioxidant, anti-inflammatory, and antitumor effects.²⁷⁰ Stimulation with COX-2 results in overexpression of PGE2, a key promotor of the expression of STAR and aromatase. Abnormal expression of STAR and aromatase will lead to high levels of estradiol production, which may promote the occurrence and development of endometriosis.² Li et al showed that UA had anti-proliferation, pro-apoptosis, and anti-angiogenesis effects. Treatment with UA significantly decreased COX-2 expression and subsequent PGE2 production in human primary endometriotic stromal cells, while significantly enhanced the expression of caspase-3. Meanwhile, VEGF was decreased after the treatment of UA. The result of capillary formation experiments also supported the inhibitory effect of UA on angiogenesis. In addition, the negative impact of UA against endometriosis may attribute to the regulation of the JNK and p38 signaling pathways.²⁷¹

Wogonin

Scutellaria baicalensis is one of the most common herbs in traditional Chinese medicine. Wogonin (WG, Figure 9), known as a kind of flavonoid, is abundantly identified from the root of Scutellaria baicalensis.^{272,273} It has a wide range of biological properties, taking antitumor,²⁷³ anti-inflammatory,²⁷⁴ and pro-apoptotic²⁷⁵ properties as examples. Estrogen enhances the proliferation and survival of endometriotic tissues.² Ferella et al investigated that WG could significantly inhibit the expression of estrogen receptor α in THESC and could induce cell cycle arrest at the G2/M phase, thereby inhibiting cell proliferation. Additionally, WG increased intracellular ROS accumulation and promoted cell apoptosis. WG significantly reduced the area of ectopic endometrial lesions in vivo.¹¹³

Discussion and Conclusion

Endometriosis is a benign disease and usually occurs in women of childbearing age.²⁷⁶ The common clinical symptoms of endometriosis are pelvic pain, discomfort during intercourse, pelvic masses, and infertility.^{12,15} The common management options in clinical practice currently are pharmacotherapy and surgery.²⁹ The majority of conventional pharmacotherapy treatments are hormonal drugs and NSAIDs. Hormonal drugs are used to induce pseudopregnancy, pseudomenopause, or suppress ovarian function.³² However, these drug treatments interfere with ovulation and prevent conception in patients of reproductive age who have reproductive needs. Hormonal drugs can generate serious adverse effects when used for a long-term treatment.^{22,24–28,31,32} Side effects such as gastrointestinal reactions and neurological symptoms may occur after the use of NSAIDs.²⁰ Even though endometriosis lesions can be surgically removed, the

disease has a high recurrence rate after surgical removal.³³ On the other hand, the ovarian cortex may be damaged during surgery, with the postoperative decline in ovarian reserve function.^{29,31} Additionally, the surgery is an invasive procedure into the abdominal cavity, which may inevitably lead to pelvic and/or abdominal adhesions. Pelvic and/or abdominal adhesions are also detrimental to the patient's pregnancy. Thus, the development of novel, effective, safe, low side effects and affordable drugs for individualized treatment is urgently needed, preferably ones that can be used for a long time.

Natural materials are a vital source for the discovery and development of new drugs. As described in [Table S3–S6](#), multi-component herbal preparations, extracts of medicinal plants, and purified compounds from plants/herbs, have been shown to target a variety of cellular processes, such as cell proliferation, apoptosis, inflammation, autophagy, oxidative stress, adhesion, migration, invasion, fibrosis, estrogen and progesterone receptor expression, and angiogenesis, which are critical in the pathogenesis of endometriosis. The anti-endometriosis effects involve plentiful molecular mechanisms and targets, including anti-proliferative (CCNE1, CDK2, and CDK4), anti-inflammatory (PGE2, COX-2, TNF- α , NO, IL-1 β , IL-6, and IL-8), anti-angiogenic (VEGF, matrix metalloproteinase and Ang-1), pro-apoptotic (Bax, Bak, Bcl-2, Bcl-xL), autophagy (Beclin 1, LC3-II/LC3-I), endoplasmic reticulum stress, endoplasmic reticulum apoptotic pathway, mitochondrial apoptotic pathway and caspase cascade, anti-migratory invasion (MMP-2, MMP-9, TIMP1, E-cadherin, N-cadherin, Snail and Slug), regulation of estrogen and progesterone receptors, and anti-fibrotic (E-calmodulin, α -SMA, type I collagen, wave proteins and fibronectin). The signaling pathways involved in these effects are mainly the Hippo pathway, TGF- β /Smad signaling pathway, NF- κ B, MAPK, PI3K/Akt, and JAK2/STAT3 signaling pathway. Medicinal plant extracts and multi-component herbal preparations contain various bioactive compounds. Therefore, they have infinite potential as multi-targets drugs. They may also affect multiple signaling pathways simultaneously, which could synergistically enhance their efficacy in the treatment of endometriosis. As mentioned above, the structural modification of bioactive lead compounds also has enormous potential to fight diseases.

Even the bioactive extracts and compounds mentioned in this review have shown interesting efficacy in the treatment of endometriosis, but most of the studies are based on preclinical cellular experiments and animal model experiments, namely, few clinical trials have been conducted. Almost all the animal experiments covered in this review were carried out in mice or rats, and these artificial animal models of endometriosis do not fully simulate the development of endometriosis, because there are obvious differences in the physiological mechanisms of reproduction between humans and animals. Therefore, more researches in the future are also needed to establish models in suitable animals, such as orangutans, which have similar physiological structures and physiological mechanisms as humans. Furthermore, serious adverse effects have not been elucidated in depth. In another aspect, most plant-derived bioactive compounds have low stability and bioavailability in vivo in their natural form, which make their effective use in patients with endometriosis challenging. More excitingly, some basic parameters of Chinese herbal medicines and natural compounds, such as chemicals, targets, oral bioavailability and blood-brain barrier, can be retrieved in the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP) ([Table S7](#)). In conclusion, more detailed comprehensive pharmacodynamic and pharmacokinetic researches are extremely necessary in the future, as well as further clinical trials to confirm the efficacy and safety of these therapeutic herbal preparations, extracts and compounds.

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Disclosure

The authors report no conflicts of interest in this work.

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