Endometriosis: A brief review of Pharmacological and Non-Pharmacological Treatment

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Abstract

Endometriosis is regarded as a spectrum disease with a wide range of subtypes and clinical manifestations. Endometriosis must be found to be present outside of (ectopic) the uterus in order to be defined histologically. These ectopic lesions are frequently found on the peritoneum and pelvic organs. They may occasionally exist in the bladder, kidneys, lungs, and even the brain, among other body organs. Regarding behavioral characteristics, research has been done on the connection between dietary preferences, alcohol and caffeine consumption, smoking, and physical activity in relation to involvement in developing endometriosis. Normal responses to progesterone in the uterine endometrium include suppression of estrogen-dependent epithelial cell proliferation, maturation of the glands' secretory systems, and differentiation of stromal cells into specialized decidual cells. Additionally, progesterone briefly produces the receptive phenotype necessary for embryo implantation in endometrial epithelial cells. Pain is one of its predominant clinical features. Women with endometriosis experience a variety of pain symptoms, most commonly dysmenorrhea, noncyclical pelvic pain, dyspareunia, and dyschezia. The experience of pain, no matter what the underlying disease, involves several different mechanisms and interactions between the periphery and the central nervous system (CNS).

Symptoms of endometriosis include: gradually increasing acute premenstrual pain, pelvic pain, pain in the sacral region of the spine, dysmenorrhea, painful ovulation, pain during intercourse, pain when defecating, pain when urinating, pain radiating to the back, abundant irregular menstruation, blood in the stool, diarrhea or constipation, infertility and chronic fatigue. The basic examination in the diagnosis of endometriosis is an ultrasound examination. Treatment of endometriosis is a big medical problem due to the fact that this disease is difficult to treat and is chronic in nature. Pharmacological, surgical or combination treatment is possible. Emerging pharmacological therapies are mostly based on targeting the molecular steps relevant for the pathogenic mechanisms or selective hormonal receptiveness. Medicinal plants and botanical products are now commonly used for managing the symptoms of numerous gynecologic disorders, for instance, endometriosis. Medicinal plants and their active compounds have displayed anti proliferative, antioxidant, analgesic, and anti-inflammatory properties. These properties may help in treating or regressing endometriosis.

Keywords: *Endometriosis, proliferative, antioxidant, analgesic, and anti-inflammatory*

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1. Introduction

Endometriosis is regarded as a spectrum disease with a wide range of subtypes and clinical manifestations. A result of this ambiguity is a significant heterogeneity in studies that have been published and are either evaluating diagnostic and therapeutic interventions in endometriosis patients generally or focusing on a specific subgroup based on a published classification or a disease subtype with a study-specific definition. Because of this variety, evidence is challenging to understand, compile, and draw conclusions about the best methods for treating endometriosis patients(Tomassetti et al. 2021). Endometriosis must be found to be present outside of (ectopic) the uterus in order to be defined histologically. These ectopic lesions are frequently found on the peritoneum and pelvic organs. They may occasionally exist in the bladder, kidneys, lungs, and even the brain, among other body organs(D'Hooghe and Debrock 2002). The condition causes severe morbidity in the affected women, including several procedures, pelvic discomfort, adnexal mass, and additional infertility. Age, race, alcohol consumption, body mass index (BMI), cigarette smoking, and menstrual characteristics (such as early menarche, menstrual length, cycle regularity, dysmenorrhea, and intensity of menstrual flow) have all been identified as risk factors for the disease(Ashish et al. 2020). There are clinically aggressive histologic subtypes of the illness, such as the serous histotype, but the majority of women who are diagnosed with endometrial cancer (EC) have well-differentiated tumours with endometrioid histology linked to early-stage disease and favourable outcomes(Dörk et al. 2020). According to earlier research, 0.3% to 1.6% of endometriosis cases may develop into cancer(Nezhat et al. 2008). The actual cause of endometriosis is still unknown, despite the fact that much knowledge about the condition has been obtained over the past few decades thanks to research programmes. It is widely acknowledged that the genetic makeup, hormonal activity, inflammatory condition, and immunological milieu all have a significant impact on how endometriosis manifests and progresses(Parasar, Ozcan, and Terry 2017). Regarding behavioural characteristics, research has

been done on the connection between dietary preferences, alcohol and caffeine consumption, smoking, and physical activity in relation to involvement in developing endometriosis(Hemmert et al. 2019). Caffeine and alcohol consumption have been suggested to affect reproductive hormones, increasing the conversion of testosterone to oestrogen, and may contribute to the pathogenesis of endometriosis(Schliep et al. 2012). In light of the potential impact of exercise on endometriosis, it has been proposed that vigorous exercise may promote endometrial proliferation by elevating oestrogen and insulin-like growth factor-1 levels(Friberg, Wallin, and Wolk 2011). Over 60,000 incident cases and 10,000 fatalities from EC occur each year in the US. After lung and colorectal cancers (CRC), its incidence is predicted to rise to over 120,000 cases by 2030, making EC the third most frequent cancer afflicting women in the US(Bokhman 1983). The second part of the nineteenth century saw the first references to the pathogenesis of endometriosis in the literature. Karl von Rokitansky first identified this syndrome in 1860, defining it as the existence of an active endometrium outside the uterine cavity(Smolarz, Szyłło, and Romanowicz 2021).

1.1. Pathophysiology:

The strongest evidence points to the so-called retrograde menstruation phenomena as the pathogenic theory(Burney and Giudice 2012). The number of ovulations and menstruations a woman experiences overall over her reproductive life span increases as her age at menarche, the number of pregnancies she has, the length of time she breastfeeds, and the timing of her first delivery all decrease. The historical norm has not been continuous monthly menstruation for decades. Therefore, it's possible that today there is a higher chance of getting a sickness that is specifically brought on by menstruation.62 In fact, having frequent and plentiful periods raises your chance of developing endometriosis(Viganò et al. 2004)(Holt and Weiss 2000)(Gylfason et al. 2010)(Simoens et al. 2012)(Nnoaham et al. 2011)(Mirkin, Murphy-Barron, and Iwasaki 2007)(Levy et al. 2011)(Burney and Giudice 2012). Seven risk loci show a strong connection with endometriosis, according to meta-analyses of the few genome-wide association studies conducted in recent years(Nyholt et al. 2012)(Pagliardini et al. 2013). The WNT4, CDKN2B-AS1, and GREB1 genes are ideal candidates for more endometriosis research because to their gene-based ranking, established pathophysiology, and closeness to single nucleotide polymorphisms with significant genome-wide effects. A member of the wingless type MMTV integration site family, encoded by WNT4, is crucial for the growth of the female reproductive system and for the production of steroids. The CDKN2B-AS1 gene is produced in a long non-coding RNA in the antisense direction of uterine contractions and is situated in the second-densest gene desert for putative enhancers in the human genome. They have the ability to implant, develop, and penetrate onto pelvic tissues once they enter the peritoneal cavity. Any monthly, reproductive, or personal characteristic that might increase pelvic contamination by regurgitated endometrium has an epidemiological impact on this event's chance(Cramer et al. 1986)(FRISCH et al. 1992)(Darrow et al. 1993). Physiologically, by any change at the molecular level that encourages the stepwise process of cell implantation and proliferation at ectopic places, such as an early age at menarche or a protracted menstrual cycle (Figure 1).

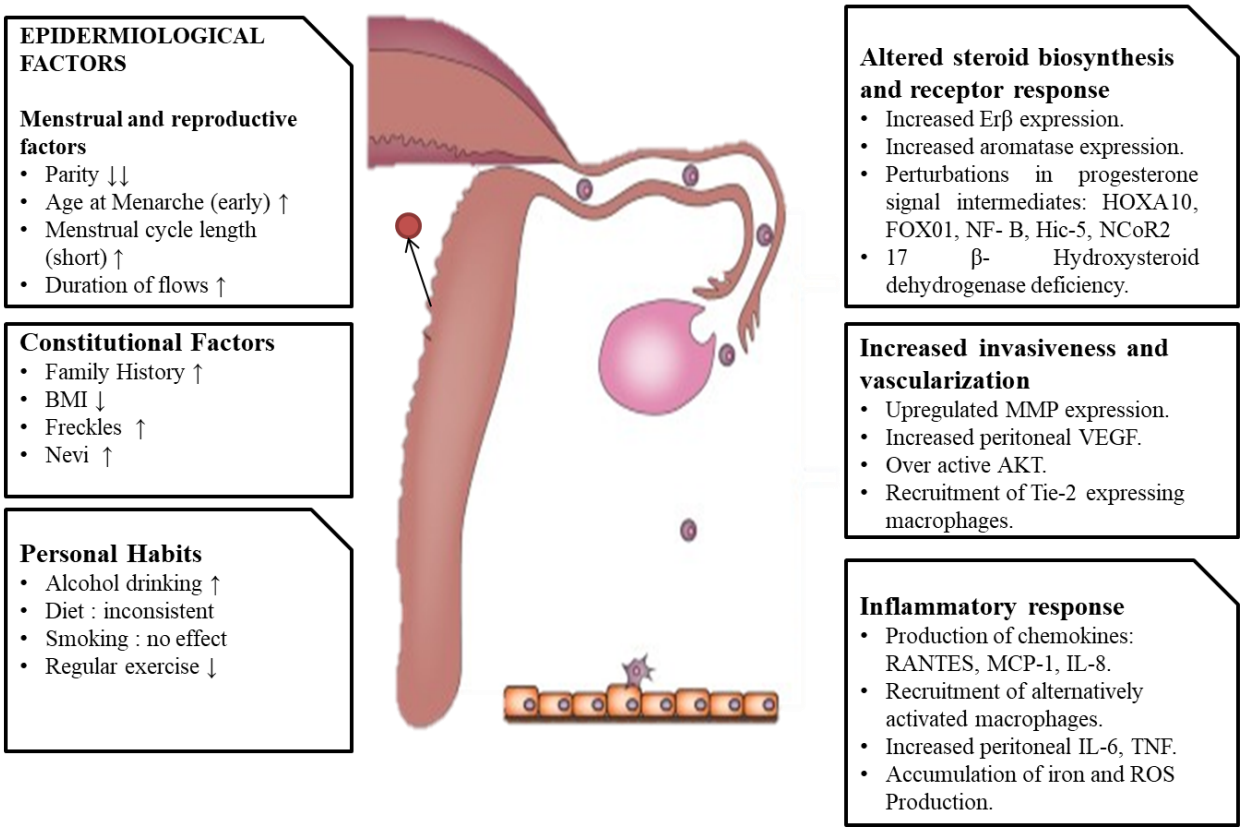

Figure 1. Endometriosis development is influenced by epidemiological variables and biological pathways. Due to a pressure gradient that may have been caused by dyssynergic uterine contractions, viable endometrial fragments are forced into the fallopian tubes during retrograde menstruation. Once within the peritoneal cavity, they have the ability to implant, develop, and infect pelvic tissues. Any menstrual, reproductive, or personal characteristic, such as an early age at menarche or a lengthy duration of each menstrual flow, that increases pelvic contamination by regurgitated endometrium, influences the risk of this happening epidemiologically. Any molecular change that encourages the gradual process of cell implantation and proliferation at ectopic sites has an impact on this event's likelihood biologically. Arrows show the direction of a danger.

Abbreviations: ERβ, estrogen receptor β; FOXO1, forkhead box O1; HOXA10, homeobox A10; MCP-1, monocyte chemotactic protein 1; MMP, matrix metalloprotease; NCoR2, nuclear receptor corepresssor 2; NF-κB, nuclear factor κB; ROS, reactive oxygen species; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

Ectopic endometrial development is fueled by oestrogens, and changes in oestrogen signalling have been linked to the condition(NA 2002). Estradiol can be created locally in endometriotic

implants via aromatase expression as well as from recognised steroidogenic organs to encourage the development of ectopic tissue(L S Noble et al. 1996)(Luis S. Noble et al. 1997). Normal responses to progesterone in the uterine endometrium include suppression of estrogen-dependent epithelial cell proliferation, maturation of the glands' secretory systems, and differentiation of stromal cells into specialized decidual cells. Additionally, progesterone briefly produces the receptive phenotype necessary for embryo implantation in endometrial epithelial cells. Progesterone resistance leads to the loss of genes necessary for these processes, such as prolactin for decidual response(L. Aghajanova et al. 2009). On the other hand, inflammation brought on by endometriosis may result in progesterone resistance by changing the progesterone signalling pathway through processes that compete with or interact with the transcriptional factors that promote inflammation. Endometriosis causes abnormalities in a number of signal intermediates, including the co-regulator Hic-5 and the chaperone protein FKBP4(Lusine Aghajanova, Velarde, and Giudice 2009)(Batt 2013).

1.3. Pain in Endometriosis

Endometriosis is an estrogen-dependent inflammatory disease estimated to affect approximately 10% of women of reproductive age. Pain is one of its predominant clinical features. Women with endometriosis experience a variety of pain symptoms, most commonly dysmenorrhea, noncyclical pelvic pain, dyspareunia, and dyschezia(Simoens et al. 2012). Endometriosis-associated pain is as complex as the 16 disease itself(Canis et al. 1997). Pain may be nociceptive (including inflammatory), neuropathic or a combination of these and it is likely that endometriosis gives rise to all three types of pain(Vercellini et al. 2014). Moreover, factors such as psychological and physical stress, hormone status and various coping mechanisms are known to influence pain perception(Nakae 2016). However, it is plausible that in an individual one particular pain mechanism may predominate, possibly due to a particular pathogenesis or disease entity and therefore symptoms may only be responsive to certain treatments(Sotome et al. 2021).
The experience of pain, no matter what the underlying disease, involves several different mechanisms and interactions between the periphery and the central nervous system (CNS)(Stratton and Berkley 2011). Recent work has shown alterations in both the peripheral and central nervous systems of women with endometriosis-associated pain, in addition to demonstrating direct innervation of endometriotic deposit(Brawn et al. 2014);(Morotti et al. 2014). Peripheral mechanisms in endometriosis-associated pain are numerous with interplay between endometriotic lesions, immune system, peripheral nerve fibres in both the lesions and adjacent peritoneum and peripheral neurons(Asante and Taylor 2011). Changes in the peritoneal fluid (PF) in women with endometriosis can activate or sensitise peripheral nociceptors(Adamson et al. 2010). Numerous algogens (pain-producing agents) have been identified in the PF of women with endometriosis, which can directly evoke excitatory inward currents or modify the function of ion channels, for example the transient receptor potential vanilloid channel 1 (TRPV1)(Rocha et al. 2011). Furthermore, cytokines (such as IL-1b, IL-6, and TNFa), growth factors (such as b-nerve growth factor and vascular endothelial growth

factor), and several chemokines, such as CCL2 (also known as monocyte chemotactic protein-1), which are secreted by immune cells, are also present at increased levels in PF of endometriosis patients. They can directly sensitise peripheral nerves through specific cell-surface receptors or evoke complex feedback loops, which amplify the microenvi ronmental inflammatory response and the generation of pain(McKinnon et al. 2015).
Brain-derived neurotrophic factor (BDNF) or neurotrophin 4 and 5 (NT4/5) suggesting a role for these neurotrophins in the modulation of endometriosis-associated innervation and related pain(Zheng, Liu, and Guo 2012);(Barcena de Arellano et al. 2013). In women with endometriosis, infertility arises mostly as the consequence of chronic pelvic inflammation(De Ziegler, Borghese, and Chapron 2010)

1.4. Endometriosis – Symptomatology

Endometriosis-related symptoms can affect a woman's overall health and mental and social well-being. It causes a significant deterioration in the quality of life(Vessey, Villard-Mackintosh, and Painter 1993);(Viganò et al. 2004). In 66% of women with endometriosis, the first symptoms of the disease appear before the age of 20(Saridoɬan 2015). Symptoms of endometriosis include: gradually increasing acute premenstrual pain, pelvic pain, pain in the sacral region of the spine, dysmenorrhea, painful ovulation, pain during intercourse, pain when defecating, pain when urinating, pain radiating to the back, abundant irregular menstruation, blood in the stool, diarrhea or constipation, infertility and chronic fatigue(Kowalczyk-Amico, Szubert, and Suzin 2009). Patients may also experience uncharacteristic accompanying symptoms such as subfebrile conditions, nausea, dizziness and headaches, symptoms of depression, anxiety, hypoglycemia, rectal bleeding, hematuria during menstruation or susceptibility to infections and allergies.
The pain associated with endometriosis most often takes the form of painful menstruation. It precedes the appearance of bleeding; over time it intensifies and its location concerns the lower abdomen and deeper pelvic areas. Pain can radiate to the sacral region. The pain can extend beyond the bleeding period and also be present throughout the menstrual cycle. There is a hypothesis that the intensification of menstruation soreness is associated with the involvement of the Douglas sinus and the formation of adhesions in it(Smolarz, Szyłło, and Romanowicz 2021).
Sometimes very advanced endometriosis may not cause any symptoms, and, paradoxically, small foci within the peritoneum can cause great pain. Intraperitoneal adhesions or overgrowth of the fallopian gouges are the most common causes of the problem with the treatment of endometriosis. Sometimes foci of endometriosis produce antibodies to the eutopic endometrium, which can induce poor embryo implantation or spontaneous abortions. Increased and profuse menstruation is one of the symptoms of endometriosis, e.g., in adenomyosis (so-called internal endometriosis)(Smolarz, Szyłło, and Romanowicz 2021).

1.5. Risk Factors for Endometriosis

- Early menarche—epidemiological studies analyzing the cycle of women with endometriosis have shown that the early first cycle (before the age of 11) is associated with the risk of endometriosis(Cramer et al. 1986);(Parazzini et al. 1995),
- Shorter than 27-day genital cycles, genital defects, including hymen overgrowth or narrowing of the cervical canal(Luna Russo, Chalif, and Falcone 2020). The risk of endometriosis is increased in women with short cycles, i.e., lasting less than 27 days, but is unrelated to the number of bleeding days and the volume of menstruation(Moen and Schei 1997),
- Low BMI,
- Small number of births,
- Caucasian race,
- Age 25–29,
- Daily consumption of alcohol in the amount of at least 10gm per day,
- Endometriosis is more often diagnosed in infertile women who are active smokers and whose body mass index (BMI) is normal or low(Molgaard, Golbeck, and Gresham 1985)

2. DIAGNOSIS

Histopathological examination clearly allows for the diagnosis of endometriosis. However, a good medical history, gynaecological examination with specula, two-handed examination, additional diagnostic tests using imaging techniques, laparoscopy and biochemical tests are helpful in the initial diagnosis of the disease. The basic examination in the diagnosis of endometriosis is an ultrasound examination(Reis, Monteiro, and Carneiro 2017). Ultrasound examination (ultrasonography, USG) is helpful in the diagnosis of endometrial cysts of the ovary and of congenital defects of the reproductive organs favoring the retrograde outflow of menstrual blood into the peritoneal cavity. In the case of endometriosis infiltrating the urinary bladder or the large intestine, it is justified to perform cystoscopy, colonorectoscopy and transrectal ultrasound examination(Leyland et al. 2010). In the case of deeply infiltrating endometriosis, the Rectal Water Contrast Transvaginal Sonography (RWC TVS) is also appropriate. The water contrast allows us to detect foci in the intestinal area and assess their progression. Deeply infiltrating endometriosis is characterized by the infiltration of endometrial cells > 5 mm below the surface of the peritoneum(Cornillie et al. 1990). Profound lesions mainly affect the posterior pelvic compartment, including the rectovaginal septum, posterior vaginal vault, utero sacral ligaments and anterior rectal wall, causing adhesions and distortions of pelvic anatomy(Chapron et al. 2006);(Seracchioli et al. 2007). In addition to the classic DIE pain syndrome (characterized by dysmenorrhea, dyspareunia, chronic pelvic pain, dystrophy and dyschesia), profound changes are associated with dysfunction of the pelvic organs and pelvic floor muscles (PFM)(Raimondo et al. 2017). A series of events or a combination of factors may contribute to the development of non-relaxing PFM in women with chronic pelvic pain, including direct or indirect (neuropathic) pelvic floor muscle injury, pelvic pain symptoms and inflammation. Evaluation of PFM by palpation or electromyography can cause pain, causing pelvic muscle spasm, which can be a

confounding factor. Transperineal ultrasound has been shown to be an important, reliable and non-invasive tool for assessing pelvic floor morphometry(Dietz 2017);(Youssef et al. 2016)
It is also helpful to have a magnetic resonance imaging (MRI) examination, but the ultrasound examination is the basic tool in the diagnosis of this disease. However, the gold standard in the diagnosis of endometriosis is laparoscopic surgery, with simultaneous confirmation in histopathological examination(Horne et al. 2019)(Ali, Pathak, and Mandal 2023).

3. TREATMENT

Treatment of endometriosis is a big medical problem due to the fact that this disease is difficult to treat and is chronic in nature(Basta et al. 2012). Pharmacological, surgical or combination treatment is possible. Emerging pharmacological therapies are mostly based on targeting the molecular steps relevant for the pathogenic mechanisms or selective hormonal receptiveness. Medications interfering with the inflammatory condition, hormone responsiveness, cell survival, proliferation, neoangiogenesis and invasion have been tested mostly in preclinical models, but also in humans(Soares et al. 2012). Some therapeutic agents are as follows:

Sr. No.	Drug	Brand Name	Dose	Side Effect	Reference
1.	Danazol	Danatrol	600 to 800 mg/day. Orally	Acne, Decrease in breast size, Oily skin or hair, vaginal dryness, burning, itching, or bleeding.	(Buttram, Belue, and Reiter 1982) (Al-Badr 2022)
2.	Progestogens (Medroxyprogesterone acetate)	PROMETRIUM	Doses ranging from 20 to 100 mg daily. Orally	Side effects include nausea (0 to 80%), breast tenderness (5%), fluid retention (50%), and depression (6%).	(Bruner et al. 1999) (Brown and Farquhar 2014)
3.	Leuprolide	Lupron Depot	7.5 mg IM monthly, 22.5 mg IM every 3 months	Transient vaginal bleeding, hot flashes, vaginal dryness, decreased libido, breast tenderness, insomnia, depression, irritability and fatigue, headache, osteoporosis, and	(Sharpe-Timms et al. 1998) (Donnez and Dolmans 2021)

				decreased skin elasticity	
4.	Gestrinone	Dimetrose	Orally in doses of 2.5 to 10 mg weekly, on a daily, twice-weekly, or three times-weekly schedule	Voice changes, hirsutism, and clitoral hypertrophy	(Cornillie et al. 1986) (Robyn, Bourdoux, and Copinschi 1983)
5.	Mifepristone	MIFEPREX	200 mg**,** orally as a single dose	Abdominal or stomach pain or uterine cramping, back pain, diarrhea, dizziness, fatigue, hypokalemia, loss of appetite	(Zhang 2016)
6.	Cetrorelix	Cetrotide	0.25 mg, subcutaneously	Injection site reactions (pain, swelling, redness), Itching, Irritation, Nausea, Vomiting, Lower abdominal pain, Ovarian hyperstimulation syndrome	(Taniguchi et al. 2013)
7.	Tanaproget	NSP-989, WAY-166989	effective dose (EC50) of 0.15 nM	Side effects such as blood clots, heart attacks, and strokes, or problems of the liver and eyes	(Bruner-Tran et al. 2006)
8.	Letrozole	Femara	2.5 mg PO qDay	Hot flushes, difficulty sleeping, tiredness and low mood	(Agarwal and Foster 2015)
9.	Anastrazole	Arimidex	1 milligram	Constipati,	(Garzon et

			(mg) once a day	Diarrhea, Nausea, Vomiting, Upset stomach, Loss of appetite, breast swelling/tenderness/pain,	al. 2020)
10.	Quinagolide	Norprolac	75 to 150 micrograms/day, Orally	Loss of appetite, Abdominal pain, Constipation or diarrhea, Insomnia, Increased water retention, Flushing.	(F. Y. Chen et al. 2019)

3.1. Medicinal Plant used in the treatment of Endometriosis

Medicinal plants and botanical products are now commonly used for managing the symptoms of numerous gynecologic disorders, for instance, endometriosis. Medicinal plants and their active compounds have displayed antiproliferative, antioxidant, analgesic, and anti-inflammatory properties. These properties may help in treating or regressing endometriosis(Reduction et al. 2021a);(Wieser et al. 2007);(Wieser et al. 2009).

Sr. No.	**Plant Name/ Biological Name/Plant part**	**Extract & Dose**	**Mechanism of Action**	**Responsible Constituents**	**References**
1.	Chamomile Tea ***Matricaria chamomilla*** Daisy (Flowers)	Hydroalcoholic extract, 2.5 mg/kg	It attenuats the protein expression and TNF-α-induced IL-8 gene expression	Apigenin	(Manach et al. 2004) (Suou et al. 2011)
2.	Danggui ***Angelica sinensis*** Apiaceae (Root)	Hydroalcoholic Extract, 4.5 g root daily	The peritoneal levels of TNF-α and IL-18 registered lower values and CA-125 decreased. It suppressed the expression of	Ferulic acid	(Jin et al. 2012) (Xiong et al. 2020)

			MMP-2 and MMP-9		
3.	Yarrow ***Achillea biebersteinii*** Asteraceae (roots, leaves, and flowers)	Ethanolic (25%) extract, 4.5 g/day	The levels of IL-6, VEGF, and TNF-α significantly decreased	Chlorogenic Acid, Caffeic Acid, Rutin, Quercetin, Luteolin, Apigenin	(Yeşilada et al. 1995) (Mazandarani, Osia, and Ghafourian 2015)
4.	Garlic ***Allium sativum*** Amaryllidaceae (Bulbs)	Hexane extract, 300 to 2,400 mg/day for 2 to 24 weeks	Reduced cellular proliferation through the reduction of VCAM-1 and ICAM-1 expression.	Quercetin, Curcumin, Resveratrol and Naringenin	(Xiao et al. 2006)
5.	Korean wormwood ***Artemisia princeps*** Asteraceae (Leaves)	methylene chloride extract, 25-30 ml	Regulate p38 and NF-kB pathways, inhibit the expression of Bcl-2, Bcl-xL, XIAP, caspase 3, caspase 8, and caspase 9	Artemisia acetate, 1,8-cineole,	(Umano et al. 2000) (Kim et al. 2013)
6.	Mongolian milkvetch ***Astragalus membranaceus*** Fabaceae (Root)	Ethanolic extract,	Decreased the concentrations of IL-2, TNF-α, estrogen and progesterone	Astragalus polysaccharide (APS), flavonoids, saponins, alkaloids	(Orkhon et al. 2018) (Reduction et al. 2021b)
7.	Turmeric ***Curcuma longa*** Zingiberaceae (Rhizomes)	Ethanolic Extract, 6 grams a day for four to seven weeks	the volume of ectopic endometriotic foci significantly decreased, inhibit the expression of MMP-9 and TNF-α, and increased the levels of TIMP-1	Curcumin	(Swarnakar and Paul 2007) (Uchio et al. 2017)

8.	Self-heal ***Prunella vulgaris*** Lamiaceae (Dried fruit spike)	Water-extracted, 0.8 20 mg/kg and 4.100 mg/kg body weight	Inhibit the p38 MAPK/ ERK signaling pathway and regulated TNF-α-induced expression	Betulinic Acid	(Psotová et al. 2003) (Park et al. 2013)
9.	Asian Bur-Reed ***Sparganium stoloniferum*** Typhaceae (Rhizomes)	Aqueous Extract, around 4 gm/day	lowered the levels of FGF-1 and VEGF,	β-sitosterol, succinic acid and daucosterol	(Sun, Wang, and Wei 2011) (Wu, Sun, and Wang 2017)
10.	Danshen ***Salvia miltiorrhiza*** Lamiaceae (Dried roots)	Ethanolic extract, 20-30 ml in solution four times daily for two	Decreased miRNA levels of angiotensinogen and angiotensin II in dorsal root ganglion neurons, Decreased the levels of IL-18, TNF-α in the peritoneal fluid	Rosmarinic Acid, Salvianolic Acid, Dihydrotanshinone, Cryptotanshinone, Tanshinone I, and Tanshinone IIA	(Z. zhen Chen and Gong 2020) (Zhou et al. 2012)

4. CONCLUSION:

Endometriosis is a fascinating condition whose mechanism is yet unknown. The understanding of the probable causes and processes that may contribute to the onset and course of the illness has advanced significantly in recent years. There is substantial evidence to support The pathophysiology and aetiology of the illness may be influenced by immunological agents like cytokines. We are only just starting to comprehend how these immunological factors may contribute to the peritoneum, endometrium, and peritoneal cavity developing the illness. Although the argument over whether endometriosis is genuinely an autoimmune illness will continue, current data clearly show that there are at least some very significant parallels between endometriosis and autoimmune disorders such as RA, Crohn's disease, and psoriasis. The essential feature of these commonalities is the increased production of cytokines like TNF-a as well as the pathologic events that are characterised by these raised levels. Even while the existing

medical treatment plans seem to be adequate, there is undoubtedly space for improvement in terms of the goal to prevent those negative and unpleasant side effects connected with the hypoestrogenic environment created by the current GnRH- treatments. It seems promising to utilise anti-TNF-a treatments to treat autoimmune illnesses. As a result, it could be justified to use comparable medicines to the management of endometriosis.

Reference:

Adamson, G David, David J Pasta, Lusine Aghajanova, Linda C. Giudice, Amy E Hamilton, J Kwintkiewicz, Kim Chi Vo, et al. 2010. "Review Article." *Fertility and Sterility*.

Agarwal, Sanjay K., and Warren G. Foster. 2015. "Reduction in Endometrioma Size with Three Months of Aromatase Inhibition and Progestin Add-Back." *BioMed Research International*. https://doi.org/10.1155/2015/878517.

Aghajanova, L., A. Hamilton, J. Kwintkiewicz, K. C. Vo, L. C. Giudice, and Robert B. Jaffe. 2009. "Steroidogenic Enzyme and Key Decidualization Marker Dysregulation in Endometrial Stromal Cells from Women with versus without Endometriosis." *Biology of Reproduction*. https://doi.org/10.1095/biolreprod.108.070300.

Aghajanova, Lusine, Michael C. Velarde, and Linda C. Giudice. 2009. "The Progesterone Receptor Coactivator Hic-5 Is Involved in the Pathophysiology of Endometriosis." *Endocrinology*. https://doi.org/10.1210/en.2009-0008.

Al-Badr, Abdullah A. 2022. "Danazol." In *Profiles of Drug Substances, Excipients and Related Methodology*. https://doi.org/10.1016/bs.podrm.2021.10.005.

Ali, Sayad Ahad, Divya Pathak, and Suraj Mandal. 2023. "INTERNATIONAL JOURNAL OF COVID-19 AND THEIR RELATIONSHIP WITH ENVIRONMENT" 14 (1): 1–5.

Asante, Albert, and Robert N. Taylor. 2011. "Endometriosis: The Role of Neuroangiogenesis." *Annual Review of Physiology*. https://doi.org/10.1146/annurev-physiol-012110-142158.

Ashish, Ashish, Kusum Kusum, Sangeeta Rai, and Royana Singh. 2020. "Endometriosis a Brief Review: Evaluation of Crucial Risk Factors and Current Treatment Regimes." *International Journal of Advances in Medicine*. https://doi.org/10.18203/2349-3933.ijam20205053.

Barcena de Arellano, Maria Luisa, Julia Arnold, Helene Lang, Giuseppe Filiberto Vercellino, Vito Chiantera, Achim Schneider, and Sylvia Mechsner. 2013. "Evidence of Neurotrophic Events Due to Peritoneal Endometriotic Lesions." *Cytokine*. https://doi.org/10.1016/j.cyto.2013.03.003.

Basta, Antoni, Aleksandra Brucka, Jarosław Górski, Bartosz Kulig, Przemysław Oszukowski, Ryszard Poręba, and Stanisław Radowicki. 2012. "Stanowisko Zespołu Ekspertów Polskiego Towarzystwa Ginekologicznego Dotyczące Diagnostyki i Metod Leczenia Endometriozy." *Ginekologia Polska*.

Batt, Ronald E. 2013. "Endometriosis: Science and Practice." *Fertility and Sterility*. https://doi.org/10.1016/j.fertnstert.2013.05.003.

Bokhman, Jan V. 1983. "Two Pathogenetic Types of Endometrial Carcinoma." *Gynecologic Oncology*. https://doi.org/10.1016/0090-8258(83)90111-7.

Brawn, Jennifer, Matteo Morotti, Krina T. Zondervan, Christian M. Becker, and Katy Vincent. 2014. "Central Changes Associated with Chronic Pelvic Pain and Endometriosis." *Human Reproduction Update*. https://doi.org/10.1093/humupd/dmu025.

Brown, Julie, and Cindy Farquhar. 2014. "Endometriosis: An Overview of Cochrane Reviews." *Cochrane Database of Systematic Reviews*. https://doi.org/10.1002/14651858.CD009590.pub2.

Bruner-Tran, Kaylon L., Zhiming Zhang, Esther Eisenberg, Richard C. Winneker, and Kevin G. Osteen. 2006. "Down-Regulation of Endometrial Matrix Metalloproteinase-3 and -7 Expression in Vitro and Therapeutic Regression of Experimental Endometriosis in Vivo by a Novel Nonsteroidal Progesterone Receptor Agonist, Tanaproget." *Journal of Clinical Endocrinology and Metabolism*. https://doi.org/10.1210/jc.2005-2024.

Bruner, Kaylon L., Esther Eisenberg, Fred Gorstein, and Kevin G. Osteen. 1999. "Progesterone and Transforming Growth Factor-β Coordinately Regulate Suppression of Endometrial Matrix Metalloproteinases in a Model of Experimental Endometriosis." *Steroids*. https://doi.org/10.1016/S0039-128X(99)00048-3.

Burney, Richard O., and Linda C. Giudice. 2012. "Pathogenesis and Pathophysiology of Endometriosis." *Fertility and Sterility*. https://doi.org/10.1016/j.fertnstert.2012.06.029.

Buttram, V. C., J. B. Belue, and R. Reiter. 1982. "Interim Report of a Study of Danazol for the Treatment of Endometriosis." *Fertility and Sterility*. https://doi.org/10.1016/S0015-0282(16)46151-0.

Canis, M., J. G. Donnez, D. S. Guzick, J. K. Halme, J. A. Rock, R. S. Schenken, and M. W. Vernon. 1997. "Revised American Society for Reproductive Medicine Classification of Endometriosis: 1996." *Fertility and Sterility*. https://doi.org/10.1016/S0015-0282(97)81391-X.

Chapron, Charles, Nicolas Chopin, Bruno Borghese, Hervé Foulot, Bertrand Dousset, Marie Cécile Vacher-Lavenu, Marco Vieira, Wael Hasan, and Alexandre Bricou. 2006. "Deeply Infiltrating Endometriosis: Pathogenetic Implications of the Anatomical Distribution." *Human Reproduction*. https://doi.org/10.1093/humrep/del079.

Chen, Fang Ying, Xi Wang, Rui Yi Tang, Zai Xin Guo, Yu Zhou Jia Deng, and Qi Yu. 2019. "New Therapeutic Approaches for Endometriosis besides Hormonal Therapy." *Chinese Medical Journal*. https://doi.org/10.1097/CM9.0000000000000569.

Chen, Zhen zhen, and Xin Gong. 2020. "Tanshinone IIA Contributes to the Pathogenesis of Endometriosis via Renin Angiotensin System by Regulating the Dorsal Root Ganglion Axon Sprouting." *Life Sciences*. https://doi.org/10.1016/j.lfs.2019.117085.

Cornillie, F. J., I. A. Brosens, G. Vasquez, and I. Riphagen. 1986. "Histologic and Ultrastructural Changes in Human Endometriotic Implants Treated with the Antiprogesterone Steroid Ethylnorgestrienone (Gestrinone) during 2 Months." *Obstetrical and Gynecological Survey*. https://doi.org/10.1097/00006254-198611000-00020.

Cornillie, F. J., D. Oosterlynck, J. M. Lauweryns, and P. R. Koninckx. 1990. "Deeply Infiltrating Pelvic Endometriosis: Histology and Clinical Significance." *Fertility and Sterility*.

https://doi.org/10.1016/S0015-0282(16)53570-5.

Cramer, Daniel W., Emery Wilson, Robert J. Stillman, Merle J. Berger, Serge Belisle, Isaac Schiff, Bruce Albrecht, Mark Gibson, Bruce V. Stadel, and Stephen C. Schoenbaum. 1986. "The Relation of Endometriosis to Menstrual Characteristics, Smoking, and Exercise." *JAMA: The Journal of the American Medical Association*. https://doi.org/10.1001/jama.1986.03370140102032.

D'Hooghe, Thomas M., and Sophie Debrock. 2002. "Endometriosis, Retrograde Menstruation and Peritoneal Inflammation in Women and in Baboons." *Human Reproduction Update*. https://doi.org/10.1093/humupd/8.1.84.

Darrow, Sherri L., John E. Vena, Ronald E. Batt, Maria A. Zielezny, Arthur M. Michalek, and Sharon Selman. 1993. "Menstrual Cycle Characteristics and the Risk of Endometriosis." *Epidemiology*. https://doi.org/10.1097/00001648-199303000-00009.

Dietz, Hans Peter. 2017. "Pelvic Floor Ultrasound: A Review." *Clinical Obstetrics and Gynecology*. https://doi.org/10.1097/GRF.0000000000000264.

Donnez, Jacques, and Marie Madeleine Dolmans. 2021. "Endometriosis and Medical Therapy: From Progestogens to Progesterone Resistance to GNRH Antagonists: A Review." *Journal of Clinical Medicine*. https://doi.org/10.3390/jcm10051085.

Dörk, Thilo, Peter Hillemanns, Clemens Tempfer, Julius Breu, and Markus C. Fleisch. 2020. "Genetic Susceptibility to Endometrial Cancer: Risk Factors and Clinical Management." *Cancers*. https://doi.org/10.3390/cancers12092407.

Friberg, Emilie, Alice Wallin, and Alicja Wolk. 2011. "Sucrose, High-Sugar Foods, and Risk of Endometrial Cancer - A Population-Based Cohort Study." *Cancer Epidemiology Biomarkers and Prevention*. https://doi.org/10.1158/1055-9965.EPI-11-0402.

FRISCH, ROSE E., GRACE WYSHAK, LEE S. ALBERT, and ARTHUR J. SOBER. 1992. "DYSPLASTIC NEVI, CUTANEOUS MELANOMA, AND GYNECOLOGIC DISORDERS." *International Journal of Dermatology*. https://doi.org/10.1111/j.1365-4362.1992.tb03948.x.

Garzon, Simone, Antonio Simone Laganà, Fabio Barra, Jvan Casarin, Antonella Cromi, Ricciarda Raffaelli, Stefano Uccella, Massimo Franchi, Fabio Ghezzi, and Simone Ferrero. 2020. "Aromatase Inhibitors for the Treatment of Endometriosis: A Systematic Review about Efficacy, Safety and Early Clinical Development." *Expert Opinion on Investigational Drugs*. https://doi.org/10.1080/13543784.2020.1842356.

Gylfason, Jon Torfi, Kristjan Andri Kristjansson, Gudlaug Sverrisdottir, Kristin Jonsdottir, Vilhjalmur Rafnsson, and Reynir Tomas Geirsson. 2010. "Pelvic Endometriosis Diagnosed in an Entire Nation over 20 Years." *American Journal of Epidemiology*. https://doi.org/10.1093/aje/kwq143.

Hemmert, Rachael, Karen C. Schliep, Sydney Willis, Charles Matthew Peterson, Germaine Buck Louis, Kristina Allen-Brady, Sara E. Simonsen, Joseph B. Stanford, Jiyoung Byun, and Ken R. Smith. 2019. "Modifiable Life Style Factors and Risk for Incident Endometriosis." *Paediatric and Perinatal Epidemiology*. https://doi.org/10.1111/ppe.12516.

Holt, V. L., and N. S. Weiss. 2000. "Recommendations for the Design of Epidemiologic Studies of Endometriosis." *Epidemiology*. https://doi.org/10.1097/00001648-200011000-00007.

Horne, A. W., J. Daniels, L. Hummelshoj, E. Cox, and K. G. Cooper. 2019. "Surgical Removal of Superficial Peritoneal Endometriosis for Managing Women with Chronic Pelvic Pain: Time for a Rethink?" *BJOG: An International Journal of Obstetrics and Gynaecology*. https://doi.org/10.1111/1471-0528.15894.

Jin, Mingliang, Ke Zhao, Qingsheng Huang, Chunlan Xu, and Peng Shang. 2012. "Isolation, Structure and Bioactivities of the Polysaccharides from Angelica Sinensis (Oliv.) Diels: A Review." *Carbohydrate Polymers*. https://doi.org/10.1016/j.carbpol.2012.04.049.

Kim, Ji Hyun, Seung Hyun Jung, Yeong In Yang, Ji Hye Ahn, Jin Gyeong Cho, Kyung Tae Lee, Nam In Baek, and Jung Hye Choi. 2013. "Artemisia Leaf Extract Induces Apoptosis in Human Endometriotic Cells through Regulation of the P38 and NFκB Pathways." *Journal of Ethnopharmacology*. https://doi.org/10.1016/j.jep.2012.12.003.

Kowalczyk-Amico, K., M. Szubert, and J. Suzin. 2009. "Angiogenesis and Inflammatory Response in Endometriosis." *Przeglad Menopauzalny*.

Levy, Adrian R., Katherine M. Osenenko, Greta Lozano-Ortega, Robert Sambrook, Mark Jeddi, Serge Bélisle, and Robert L. Reid. 2011. "Economic Burden of Surgically Confirmed Endometriosis in Canada." *Journal of Obstetrics and Gynaecology Canada*. https://doi.org/10.1016/S1701-2163(16)34986-6.

Leyland, Nicholas, Robert Casper, Philippe Laberge, Sukhbir S. Singh, Lisa Allen, Kristina Arendas, Catherine Allaire, et al. 2010. "Endometriosis: Diagnosis and Management." *Journal of Obstetrics and Gynaecology Canada*. https://doi.org/10.1016/S1701-2163(16)34589-3.

Luna Russo, Miguel A., Julia N. Chalif, and Tommaso Falcone. 2020. "Clinical Management of Endometriosis." *Minerva Ginecologica*. https://doi.org/10.23736/S0026-4784.20.04544-X.

Manach, Claudine, Augustin Scalbert, Christine Morand, Christian Rémésy, and Liliana Jiménez. 2004. "Polyphenols: Food Sources and Bioavailability." *American Journal of Clinical Nutrition*. https://doi.org/10.1093/ajcn/79.5.727.

Mazandarani, Masoumeh, Nargess Osia, and Mohammad Ghafourian. 2015. "Antioxidant Activity and Ethno Pharmacological Survey of Achillea Biebersteinii Afan. In the Treatment of Dysmenorrhoea in Traditional Medicine of Golestan Province, Iran." *International Journal of Women's Health and Reproduction Sciences*. https://doi.org/10.15296/ijwhr.2015.21.

McKinnon, Brett D., Dominic Bertschi, Nick A. Bersinger, and Michael D. Mueller. 2015. "Inflammation and Nerve Fiber Interaction in Endometriotic Pain." *Trends in Endocrinology and Metabolism*. https://doi.org/10.1016/j.tem.2014.10.003.

Mirkin, David, Catherine Murphy-Barron, and Kosuke Iwasaki. 2007. "Actuarial Analysis of Private Payer Administrative Claims Data for Women with Endometriosis." *Journal of Managed Care Pharmacy*. https://doi.org/10.18553/jmcp.2007.13.3.262.

Moen, Mette Haase, and Berit Schei. 1997. "Epidemiology of Endometriosis in a Norwegian

County." *Acta Obstetricia et Gynecologica Scandinavica*. https://doi.org/10.3109/00016349709024584.

Molgaard, C. A., A. L. Golbeck, and L. Gresham. 1985. "Current Concepts in Endometriosis." *Western Journal of Medicine*.

Morotti, Matteo, Katy Vincent, Jennifer Brawn, Krina T. Zondervan, and Christian M. Becker. 2014. "Peripheral Changes in Endometriosis-Associated Pain." *Human Reproduction Update*. https://doi.org/10.1093/humupd/dmu021.

NA. 2002. "Textbook Section 15.1 Seven-Transmembrane-Helix Receptors Change Conformation in Response to Ligand Binding and Activate G Proteins." *Ncbi.Nlm*.

Nakae, Aya. 2016. "Mechanisms of Pain." In *Cognitive Neuroscience Robotics B: Analytic Approaches to Human Understanding*. https://doi.org/10.1007/978-4-431-54598-9_6.

Nezhat, Farr, M. Shoma Datta, Veneta Hanson, Tanja Pejovic, Ceana Nezhat, and Camran Nezhat. 2008. "The Relationship of Endometriosis and Ovarian Malignancy: A Review." *Fertility and Sterility*. https://doi.org/10.1016/j.fertnstert.2008.08.007.

Nnoaham, Kelechi E., Lone Hummelshoj, Premila Webster, Thomas D'Hooghe, Fiorenzo De Cicco Nardone, Carlo De Cicco Nardone, Crispin Jenkinson, Stephen H. Kennedy, and Krina T. Zondervan. 2011. "Impact of Endometriosis on Quality of Life and Work Productivity: A Multicenter Study across Ten Countries." *Fertility and Sterility*. https://doi.org/10.1016/j.fertnstert.2011.05.090.

Noble, L S, E R Simpson, A Johns, and S E Bulun. 1996. "Aromatase Expression in Endometriosis." *The Journal of Clinical Endocrinology & Metabolism*. https://doi.org/10.1210/jcem.81.1.8550748.

Noble, Luis S., Kazuto Takayama, Khaled M. Zeitoun, J. Michael Putman, D. Alan Johns, Margaret M. Hinshelwood, Veena R. Agarwal, Ying Zhao, Bruce R. Carr, and Serdar E. Bulun. 1997. "Prostaglandin E2 Stimulates Aromatase Expression in Endometriosis-Derived Stromal Cells." *Journal of Clinical Endocrinology and Metabolism*. https://doi.org/10.1210/jc.82.2.600.

Nyholt, Dale R., Siew Kee Low, Carl A. Anderson, Jodie N. Painter, Satoko Uno, Andrew P. Morris, Stuart MacGregor, et al. 2012. "Genome-Wide Association Meta-Analysis Identifies New Endometriosis Risk Loci." *Nature Genetics*. https://doi.org/10.1038/ng.2445.

Orkhon, Banzragchgarav, Kyoko Kobayashi, Batkhuu Javzan, and Kenroh Sasaki. 2018. "Astragalus Root Induces Ovarian β-Oxidation and Suppresses Estrogen-Dependent Uterine Proliferation." *Molecular Medicine Reports*. https://doi.org/10.3892/mmr.2018.9493.

Pagliardini, Luca, Davide Gentilini, Paola Vigano, Paola Panina-Bordignon, Mauro Busacca, Massimo Candiani, and Anna Maria Di Blasio. 2013. "An Italian Association Study and Meta-Analysis with Previous GWAS Confirm WNT4, CDKN2BAS and FN1 as the First Identified Susceptibility Loci for Endometriosis." *Journal of Medical Genetics*. https://doi.org/10.1136/jmedgenet-2012-101257.

Parasar, Parveen, Pinar Ozcan, and Kathryn L. Terry. 2017. "Endometriosis: Epidemiology,

Diagnosis and Clinical Management." *Current Obstetrics and Gynecology Reports*. https://doi.org/10.1007/s13669-017-0187-1.

Parazzini, F., M. Ferraroni, L. Fedele, L. Bocciolone, S. Rubessa, and A. Riccardi. 1995. "Pelvic Endometriosis: Reproductive and Menstrual Risk Factors at Different Stages in Lombardy, Northern Italy." *Journal of Epidemiology and Community Health*. https://doi.org/10.1136/jech.49.1.61.

Park, Sun Haeng, Hyun Jung Koo, Yoon Young Sung, and Ho Kyoung Kim. 2013. "The Protective Effect of Prunella Vulgaris Ethanol Extract against Vascular Inflammation in TNF-α-Stimulated Human Aortic Smooth Muscle Cells." *BMB Reports*. https://doi.org/10.5483/BMBRep.2013.46.7.214.

Psotová, Jitka, Milan Kolář, Jaromír Soušek, Zdeněk Švagera, Jaroslav Vičar, and Jitka Ulrichová. 2003. "Biological Activities of Prunella Vulgaris Extract." *Phytotherapy Research*. https://doi.org/10.1002/ptr.1324.

Raimondo, D., A. Youssef, M. Mabrouk, S. Del Forno, V. Martelli, G. Pilu, N. Rizzo, L. Zannoni, R. Paradisi, and R. Seracchioli. 2017. "Pelvic Floor Muscle Dysfunction on 3D/4D Transperineal Ultrasound in Patients with Deep Infiltrating Endometriosis: A Pilot Study." *Ultrasound in Obstetrics and Gynecology*. https://doi.org/10.1002/uog.17323.

Reduction, Drudgery, Acceptability Of, Drudgery Reducing, Tool In, and O F Dairy Animals. 2021a. "Plant Archives" 21 (table 1): 2184–85. https://doi.org/10.51470/PLANTARCHIVES.2021.v21.no2.085.

———. 2021b. "Plant Archives" 21 (table 1): 2184–85.

Reis, Fernando, Cecília Monteiro, and Márcia Carneiro. 2017. "Biomarkers of Pelvic Endometriosis." *Revista Brasileira de Ginecologia e Obstetrícia / RBGO Gynecology and Obstetrics*. https://doi.org/10.1055/s-0037-1601398.

Robyn, C., P. Bourdoux, and G. Copinschi. 1983. "459 The Endocrine Effects of Gestrinone." *Journal of Steroid Biochemistry*. https://doi.org/10.1016/0022-4731(83)91960-x.

Rocha, Marcelo Gondim, Júlio César Rosa E. Silva, Alfredo Ribeiro Da Silva, Francisco José Candido Dos Reis, Antonio Alberto Nogueira, and Omero Benedicto Poli-Neto. 2011. "TRPV1 Expression on Peritoneal Endometriosis Foci Is Associated with Chronic Pelvic Pain." *Reproductive Sciences*. https://doi.org/10.1177/1933719110391279.

Saridoɬan, Ertan. 2015. "Endometriosis in Teenagers." *Women's Health*. https://doi.org/10.2217/whe.15.58.

Schliep, Karen C., Enrique F. Schisterman, Sunni L. Mumford, Anna Z. Pollack, Cuilin Zhang, Aijun Ye, Joseph B. Stanford, Ahmad O. Hammoud, Christina A. Porucznik, and Jean Wactawski-Wende. 2012. "Caffeinated Beverage Intake and Reproductive Hormones among Premenopausal Women in the BioCycle Study." *American Journal of Clinical Nutrition*. https://doi.org/10.3945/ajcn.111.021287.

Seracchioli, R., G. Poggioli, F. Pierangeli, L. Manuzzi, B. Gualerzi, L. Savelli, V. Remorgida, M. Mabrouk, and S. Venturoli. 2007. "Surgical Outcome and Long-Term Follow up after Laparoscopic Rectosigmoid Resection in Women with Deep Infiltrating Endometriosis."

BJOG: An International Journal of Obstetrics and Gynaecology. https://doi.org/10.1111/j.1471-0528.2007.01363.x.

Sharpe-Timms, Kathy L., Randall L. Zimmer, Wendy J. Jolliff, Jean A. Wright, Warren B. Nothnick, and Thomas E. Curry. 1998. "Gonadotropin-Releasing Hormone Agonist (GnRH-a) Therapy Alters Activity of Plasminogen Activators, Matrix Metalloproteinases, and Their Inhibitors in Rat Models for Adhesion Formation and Endometriosis: Potential GnRH-a- Regulated Mechanisms Reducing Adhe." *Fertility and Sterility*. https://doi.org/10.1016/S0015-0282(98)00032-6.

Simoens, Steven, Gerard Dunselman, Carmen Dirksen, Lone Hummelshoj, Attila Bokor, Iris Brandes, Valentin Brodszky, et al. 2012. "The Burden of Endometriosis: Costs and Quality of Life of Women with Endometriosis and Treated in Referral Centres." *Human Reproduction*. https://doi.org/10.1093/humrep/des073.

Smolarz, Beata, Krzysztof Szyłło, and Hanna Romanowicz. 2021. "Endometriosis: Epidemiology, Classification, Pathogenesis, Treatment and Genetics (Review of Literature)." *International Journal of Molecular Sciences*. https://doi.org/10.3390/ijms221910554.

Soares, Sérgio Reis, Alicia Martínez-Varea, Juan José Hidalgo-Mora, and Antonio Pellicer. 2012. "Pharmacologic Therapies in Endometriosis: A Systematic Review." *Fertility and Sterility*. https://doi.org/10.1016/j.fertnstert.2012.07.1120.

Sotome, S, A Sawada, A Wada, H Shima, G Kutomi, M Yamakage, T Wang, et al. 2021. "Naldebain for Control of Post-Cesarean Section Pain." *Pain Physician*.

Stratton, Pamela, and Karen J. Berkley. 2011. "Chronic Pelvic Pain and Endometriosis: Translational Evidence of the Relationship and Implications." *Human Reproduction Update*. https://doi.org/10.1093/humupd/dmq050.

Sun, Jie, Shao Wang, and Ya Hui Wei. 2011. "Reproductive Toxicity of Rhizoma Sparganii (Sparganium Stoloniferum Buch.-Ham.) in Mice: Mechanisms of Anti-Angiogenesis and Anti-Estrogen Pharmacologic Activities." *Journal of Ethnopharmacology*. https://doi.org/10.1016/j.jep.2011.08.026.

Suou, Kana, Fuminori Taniguchi, Yukiko Tagashira, Tomoiki Kiyama, Naoki Terakawa, and Tasuku Harada. 2011. "Apigenin Inhibits Tumor Necrosis Factor α-Induced Cell Proliferation and Prostaglandin E2 Synthesis by Inactivating NFκB in Endometriotic Stromal Cells." *Fertility and Sterility*. https://doi.org/10.1016/j.fertnstert.2010.09.046.

Swarnakar, Snehasikta, and Sumit Paul. 2007. "Curcumin Arrests Endometriosis by Downregulation of Matrix Metalloproteinase-9 Activity." *Indian Journal of Geo-Marine Sciences*.

Taniguchi, Fuminori, Hiroko Higaki, Yukihiro Azuma, Imari Deura, Tomio Iwabe, Tasuku Harada, and Naoki Terakawa. 2013. "Gonadotropin-Releasing Hormone Analogues Reduce the Proliferation of Endometrial Stromal Cells but Not Endometriotic Cells." *Gynecologic and Obstetric Investigation*. https://doi.org/10.1159/000343748.

Tomassetti, Carla, Neil P. Johnson, John Petrozza, Mauricio S. Abrao, Jon I. Einarsson, Andrew

W. Horne, Ted T.M. Lee, et al. 2021. "An International Terminology for Endometriosis, 2021." *Journal of Minimally Invasive Gynecology*. https://doi.org/10.1016/j.jmig.2021.08.032.

Uchio, Ryusei, Yohei Higashi, Yusuke Kohama, Kengo Kawasaki, Takashi Hirao, Koutarou Muroyama, and Shinji Murosaki. 2017. "A Hot Water Extract of Turmeric (Curcuma Longa) Suppresses Acute Ethanol-Induced Liver Injury in Mice by Inhibiting Hepatic Oxidative Stress and Inflammatory Cytokine Production." *Journal of Nutritional Science*. https://doi.org/10.1017/jns.2016.43.

Umano, K., Y. Hagi, K. Nakahara, A. Shoji, and T. Shibamoto. 2000. "Volatile Chemicals Identified in Extracts from Leaves of Japanese Mugwort (Artemisia Princeps Pamp.)." *Journal of Agricultural and Food Chemistry*. https://doi.org/10.1021/jf0001738.

Vercellini, Paolo, Paola Viganò, Edgardo Somigliana, and Luigi Fedele. 2014. "Endometriosis: Pathogenesis and Treatment." *Nature Reviews Endocrinology*. https://doi.org/10.1038/nrendo.2013.255.

Vessey, M. P., L. Villard-Mackintosh, and R. Painter. 1993. "Epidemiology of Endometriosis in Women Attending Family Planning Clinics." *British Medical Journal*. https://doi.org/10.1136/bmj.306.6871.182.

Viganò, Paola, Fabio Parazzini, Edgardo Somigliana, and Paolo Vercellini. 2004. "Endometriosis: Epidemiology and Aetiological Factors." *Best Practice and Research: Clinical Obstetrics and Gynaecology*. https://doi.org/10.1016/j.bpobgyn.2004.01.007.

Wieser, Fritz, Misha Cohen, Andrew Gaeddert, Jie Yu, Carla Burks-Wicks, Sarah L. Berga, and Robert N. Taylor. 2007. "Evolution of Medical Treatment for Endometriosis: Back to the Roots?" *Human Reproduction Update*. https://doi.org/10.1093/humupd/dmm015.

Wieser, Fritz, Jie Yu, John Park, Andrew Gaeddert, Misha Cohen, Jean Louis Vigne, and Robert N. Taylor. 2009. "A Botanical Extract from Channel Flow Inhibits Cell Proliferation, Induces Apoptosis, and Suppresses CCL5 in Human Endometriotic Stromal Cells." *Biology of Reproduction*. https://doi.org/10.1095/biolreprod.108.075069.

Wu, Yi zhou, Jie Sun, and Yu bang Wang. 2017. "Selective Estrogen Receptor Modulator: A Novel Polysaccharide from Sparganii Rhizoma Induces Apoptosis in Breast Cancer Cells." *Carbohydrate Polymers*. https://doi.org/10.1016/j.carbpol.2017.01.062.

Xiao, Dong, Mengfeng Li, Anna Herman-Antosiewicz, Jedrzej Antosiewicz, Hui Xiao, Karen L. Lew, Yan Zeug, Stanley W. Marynowski, and Shivendra V. Singh. 2006. "Diallyl Trisulfide Inhibits Angiogenic Features of Human Umbilical Vein Endothelial Cells by Causing Akt Inactivation and Down-Regulation of VEGF and VEGF-R2." *Nutrition and Cancer*. https://doi.org/10.1207/s15327914nc5501_12.

Xiong, Qi Xiang, Xiao Yun Ruan, Ai Ping Deng, Jue Liu, and Qing Zhou. 2020. "Anti-Endometriotic Effect of Angelica Sinensis (Oliv.) Diels Extract in Human Endometriotic Cells and Rats." *Tropical Journal of Pharmaceutical Research*. https://doi.org/10.4314/tjpr.v19i4.20.

Yeşilada, Erdem, Gisho Honda, Ekrem Sezik, Mamoru Tabata, Tetsuro Fujita, Toshihiro Tanaka,

Yoshio Takeda, and Yoshihisa Takaishi. 1995. "Traditional Medicine in Turkey. V. Folk Medicine in the Inner Taurus Mountains." *Journal of Ethnopharmacology*. https://doi.org/10.1016/0378-8741(95)01241-5.

Youssef, A., E. Montaguti, O. Sanlorenzo, L. Cariello, G. Salsi, G. Morganelli, C. Azzarone, G. Pilu, and N. Rizzo. 2016. "Reliability of New Three-Dimensional Ultrasound Technique for Pelvic Hiatal Area Measurement." *Ultrasound in Obstetrics and Gynecology*. https://doi.org/10.1002/uog.14933.

Zhang, Y. X. 2016. "Effect of Mifepristone in the Different Treatments of Endometriosis." *Clinical and Experimental Obstetrics and Gynecology*. https://doi.org/10.12891/ceog2086.2016.

Zheng, Yu, Xishi Liu, and Sun Wei Guo. 2012. "Therapeutic Potential of Andrographolide for Treating Endometriosis." *Human Reproduction*. https://doi.org/10.1093/humrep/des063.

Zhou, Zan Hua, Qing Weng, Jian Hong Zhou, and Jue Zhou. 2012. "Extracts of Salvia Miltiorrhiza Bunge on the Cytokines of Rat Endometriosis Models." *African Journal of Traditional, Complementary and Alternative Medicines*. https://doi.org/10.4314/ajtcam.v9i3.2.

Ziegler, Dominique De, Bruno Borghese, and Charles Chapron. 2010. "Endometriosis and Infertility: Pathophysiology and Management." *The Lancet*. https://doi.org/10.1016/S0140-6736(10)60490-4.