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Plants as source of new therapies for endometriosis: a review of preclinical and clinical studies

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BACKGROUND: Given the disadvantages and limitations of current endometriosis therapy, there is a progressive increase in studies focusing on plant-derived agents as a natural treatment option with the intention of achieving high efficiency, avoiding adverse effects and preserving the chance for successful pregnancy. The heterogeneity of these studies in terms of evaluated agents, applied approaches and outcomes illustrates the need for an up-to-date summary and critical view on this rapidly growing field in endometriosis research.

OBJECTIVE AND RATIONALE: This review provides a comprehensive overview of plant-derived agents and natural treatment strategies that are under preclinical or clinical investigation and critically evaluates their potential for future endometriosis therapy.

SEARCH METHODS: An English language PubMed literature search was performed using variations of the terms 'endometriosis', 'natural therapy', 'herb/herbal', 'plant', 'flavonoid', 'polyphenol', 'phytochemical', 'bioactive', 'Kampo' and 'Chinese medicine'. It included both animal and human studies. Moreover, the Clinicaltrials.gov database was searched with the term 'endometriosis' for clinical trials on plant-derived agents. No restriction was set for the publication date.

OUTCOMES: Natural therapies can be assigned to three categories: (i) herbal extracts, (ii) specific plant-derived bioactive compounds and (iii) Chinese herbal medicine (CHM). Agents of the first category have been shown to exert anti-proliferative, anti-inflammatory, anti-angiogenic and anti-oxidant effects on endometrial cells and endometriotic lesions. However, the existing evidence supporting their use in endometriosis therapy is quite limited. The most studied specific plant-derived bioactive compounds are resveratrol, epigallocatechin-3-gallate, curcumin, puerarin, ginsenosides, xanthohumol, 4-hydroxybenzyl alcohol, quercetin, apigenin, carnosic acid, rosmarinic acid, wogonin, baicalein, parthenolide, andrographolide and cannabinoids, with solid evidence about their inhibitory activity in experimental endometriosis models. Their mechanisms of action include pleiotropic effects on known signalling effectors: oestrogen receptor-α, cyclooxygenase-2, interleukin-1 and -6, tumour necrosis factor-α, intercellular adhesion molecule-1, vascular endothelial growth factor, nuclear factor-kappa B, matrix metalloproteinases as well as reactive oxygen species (ROS) and apoptosis-related proteins. Numerous studies suggest that treatment with CHM is a good choice for endometriosis management. Even under clinical conditions, this approach has already been shown to decrease the size of endometriotic lesions, alleviate chronic pelvic pain and reduce postoperative recurrence rates.

WIDER IMPLICATIONS: The necessity to manage endometriosis as a chronic disease highlights the importance of identifying novel and affordable long-term safety therapeutics. For this purpose, natural plant-derived agents represent promising candidates. Many of these agents exhibit a pleiotropic action profile, which simultaneously inhibits fundamental processes in the pathogenesis of endometriosis, such as proliferation, inflammation, ROS formation and angiogenesis. Hence, their inclusion into multimodal treatment concepts may essentially contribute to increase the therapeutic efficiency and reduce the side effects of future endometriosis therapy.

Key words: endometriosis / natural therapy / herb / plant / flavonoid / polyphenol / phytochemical / bioactive / Chinese herbal medicine

Introduction

Endometriosis is a common oestrogen-dependent gynecological disease, which is characterised by the presence of endometrial tissue outside the uterine cavity. The condition affects 5–10% of women of reproductive age and is usually associated with inflammation, severe pelvic pain and infertility (Burney and Giudice, 2012; Zondervan *et al.*, 2018). Moreover, endometriosis is a leading cause of miscarriage (Lessey *et al.*, 2013; Santulli *et al.*, 2016) and implantation failure (Margalioth *et al.*, 2006; Tomassetti *et al.*, 2006).

The eutopic endometrium of endometriosis patients differs from that of disease-free women and exhibits intrinsic characteristics that stimulate cell survival outside the uterine cavity (Liu and Lang, 2011). This supports the 'retrograde menstruation theory' of Sampson, postulating that eutopic endometrium gives rise to ectopic endometriotic lesions (Sampson, 1927). Pathological alterations in the endometrium of endometriosis patients may further explain the increased infertility rates associated with the disease. In fact, besides poor oocyte quality, women with endometriosis exhibit decreased uterine receptivity and abnormal expression of endometrial biomarkers (Kao *et al.*, 2003; Vassiliadis *et al.*, 2005; Liu and Lang, 2011).

The formation and survival of endometriotic lesions at ectopic sites is crucially dependent on fundamental biological processes, including proliferation, apoptosis, inflammation and angiogenesis (Nasu *et al.*, 2009; Hey-Cunningham *et al.*, 2013; Laganà *et al.*, 2019) (Fig. 1). Cell proliferation is increased in newly developing endometriotic lesions when compared to eutopic endometrium (Rosa-e-Silva et al., 2010). In addition, endometrial tissue from women with endometriosis is more resistant to apoptosis (Meresman *et al.*, 2000; Dmowski *et al.*, 2001; Szymanowski, 2007; Reis *et al.*, 2013; Roshangar *et al.*, 2013; Aznaurova *et al.*, 2014). This imbalance between proliferation and cell death promotes uncontrolled tissue growth. Endometriosis is also associated with inflammation in both the eutopic endometrium and the peritoneal cavity, characterised by altered humoral immunological function and enhanced numbers of activated peritoneal immune cells (Lousse *et al.*, 2010, 2012). This not only contributes to the

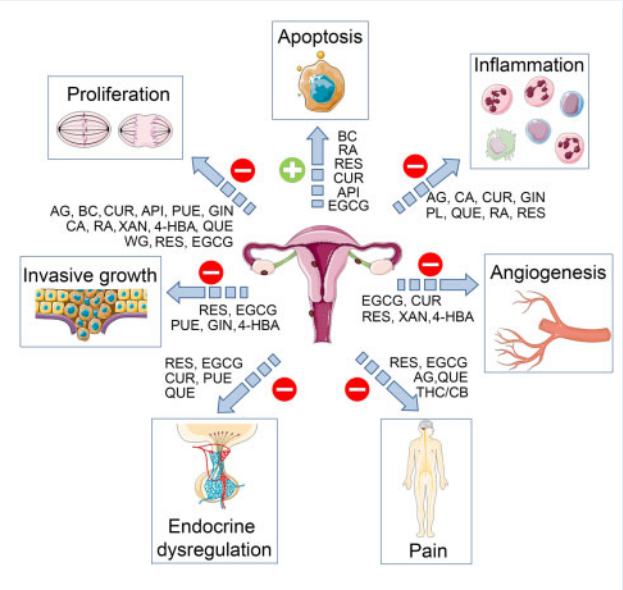

Figure 1. Targeting of dysregulated physiological processes in endometriosis by plant-derived bioactive compounds. Several physiological processes are dysregulated in endometriosis. Increased proliferation, invasion, inflammation and angiogenesis, resistance to apoptosis and dysregulation of steroid signalling contribute to lesion growth and hyperalgesia. As discussed in this review, several of these processes can be inhibited ('−' symbol) or promoted ('+' symbol; apoptosis) by plant-derived bioactive compounds. See text and Table II for details. AG, andrographolide; API, apigenin; BC, baicalein; CA, carnosic acid; CUR, curcumin; EGCG, epigallocatechin-3-gallate; GIN, ginsenosides; 4-HBA, 4-hydroxybenzyl alcohol; PL, parthenolide; PUE, puerarin; QUE, quercetin; RA, rosmarinic acid; RES, resveratrol; THC/CB, cannabinoids; WG, wogonin; XAN, xanthohumol.

persistence of ectopic endometriotic tissue against immunological defence mechanisms but also affects endometrial receptivity and pregnancy outcomes (Tomassetti *et al.*, 2006; Capobianco and Rovere-Querini, 2013). Another important hallmark in the pathogenesis of endometriosis is angiogenesis (Becker and D'Amato, 2007; Laschke and Menger, 2018). The ingrowth of new microvessels into ectopic endometrial tissue is a major prerequisite for its survival and growth (Groothuis *et al.*, 2005; Taylor *et al.*, 2009; Cho *et al.*, 2012). Accordingly, anti-angiogenic therapy has been shown to inhibit the development of experimental endometriosis (Laschke and Menger, 2007; Ricci *et al.*, 2011).

There is a close interaction of steroid hormones, the immune system and angiogenic pathways in the regulation of the aforementioned cellular processes in endometriosis (Gazvani and Templeton, 2002; Greene *et al.*, 2016). The peritoneal fluid from patients with endometriosis contains high levels of vascular endothelial growth factor (VEGF), which is released by both endometriotic lesions and peritoneal macrophages (Takehara *et al.*, 2004; Bourlev *et al.*, 2006). It has been further reported that VEGF induces cyclooxygenase-2 (COX-2) expression in endometrial and endometriotic cells (Attar and Bulun, 2006; Attar *et al.*, 2009; Bulun *et al.*, 2015). Oestrogen and COX-2, in turn, enhance the expression of VEGF and matrix metalloproteinases (MMPs), which are also involved in angiogenesis. This vicious cycle finally maintains elevated concentrations of prostaglandin E_2 (PGE_2), a known mediator of active inflammation and pain in endometriotic tissue (Attar and Bulun, 2006) (Fig. 1).

The induction of hypoestrogenemia by combined oral contraceptives, progestins or gonadotropin releasing hormone agonists (GnRHa) is currently the most common pharmacological approach for the therapy of endometriosis. However, this type of treatment is unsatisfactory due to its side effects. Another option is the surgical removal of endometriotic lesions, which, however, is associated with high recurrence rates of up to 50% within 5 years of surgery (Guo, 2009; Guo and Martin, 2019).

Hence, it is of major importance to establish improved strategies for the management of endometriosis. To achieve this, an increasing number of studies focus on plant-derived agents as a natural treatment option with the intention of achieving high efficiency, avoiding adverse effects and preserving the chance for successful pregnancy. The present review provides a comprehensive overview of these agents and natural treatment strategies that are currently under preclinical or clinical investigation and critically evaluates their potential for future endometriosis therapy.

Methods

Articles were selected for relevance and quality from the English language PubMed literature database. The search was performed using variations of the terms 'endometriosis', 'natural therapy', 'herb/herbal', 'plant', 'flavonoid', 'polyphenol', 'phytochemical', 'bioactive', 'Kampo' and 'Chinese medicine'. It included both animal and human studies. Moreover, the Clinicaltrials.gov database was searched with the term 'endometriosis' for clinical trials on plant-derived agents. No restriction was set for the publication date.

Herbal Extracts

Phytomedicine has been practiced worldwide since ancient times to treat or alleviate human disease. Herbal extracts are highly complex multi-component mixtures. Hence, synergistic actions of their individual components may be highly beneficial (Zhou *et al.*, 2016). Accordingly, they have also been evaluated in different *in vitro* and *in vivo* models of endometriosis.

Pueraria flower extract

Pueraria lobata, also known as 'Kudzu', is a perennial leguminous plant consumed as a functional food in East Asia countries. Puerarin, one of the major isoflavones of the plant, is anti-oxidative and anti-inflammatory and inhibits aromatase activity in endometrial cells (Li *et al.*, 2008; Chen *et al.*, 2018a). Referring specifically to the herbal extract, the effects of pueraria flower extract (PFE) have been assessed on experimental endometriosis both *in vitro* and *in vivo*. It was found that PFE reduces MMP-2 and MMP-9 mRNA and protein levels in endometriotic cells and suppresses their adhesion and migration (Kim *et al.*, 2017). Moreover, mice, which were orally treated with PFE for

5 weeks beginning 1 week before the inoculation of endometrial fragments, exhibited a reduced number of newly developing endometriotic lesions when compared to vehicle-treated controls (Kim et al., 2017). These results suggest that PFE has potential as a therapy for preventing and treating endometriosis.

Hexane extract of aged black garlic

Garlic (*Allium sativum*) is a plant commonly used in many cultures of the world. It is one of the most widely researched medicinal plants that has been used as spice, food and medicine for over four thousand years. Extensive research has been carried out on the beneficial properties of garlic and its effects on various pathologies (Thomson and Ali, 2003). Moreover, different formulations of garlic have been developed. One of the most useful garlic preparations is aged black garlic. Several studies have shown that the extracts of aged black garlic exhibit a broad pharmacological effect spectrum, including pro-apoptotic, anti-oxidant and anti-cancer activity (Thomson and Ali, 2003; Park et al., 2014). Recently, Kim et al. (2013) suggested that hexane extract of aged black garlic (HEABG) to be effective in the prevention and treatment of endometriosis. They found that HEABG inhibits cell proliferation and cell cycle progression of tumour necrosis factor (TNF)-α-activated human endometriotic stromal cells isolated from patients with ovarian endometrioma through inhibition of the ERK and JNK signalling pathways (Kim et al., 2013). In addition, treatment of endometriotic stromal cells with HEABG potently suppressed TNF-α-induced intercellular adhesion molecule (ICAM)-1 and vascular adhesion molecule (VCAM)-1 expression by inhibiting the activation of nuclear factor-kappa B (NF-κB) and nuclear activator protein-1 transcription factors (Kim et al., 2013). The latter mechanism may inhibit the recruitment of immune cells into endometriotic lesions and, thus, contribute to reduce disease-associated inflammation.

Uncaria tomentosa extract

Cat's claw is a specific plant from the Amazon rain forest. It is named after its leafy pattern that resembles the claws of a cat. There are several species of cat's claw, but the two most common varieties used are *Uncaria tomentosa* and *U. guianensis*. *U. tomentosa* is clearly the preferred variety because of its higher alkaloid content and the ease of standardisation (Erowele and Kalejaiye, 2009). Diseases which have been successfully treated with *U. tomentosa* include rheumatoid arthritis, prostatitis and cancer (Della Valle, 2017). The plant exerts anti-oxidant and anti-inflammatory effects mediated by the inhibition of PGE_2. In addition, it can alter cell cycle progression by inducing apoptosis (Neto et al., 2011). In rats with surgically induced endometriosis, *Uncaria tomentosa* extract (UTE) reduced the growth of ectopic lesions when compared to controls (Neto et al., 2011).

Açai extract

Açai, the fruit of an Amazonian plant, is a berry grown on the palm tree *Euterpe oleracea*. In the last years, research on the açai fruit has focused on its anti-oxidant, anti-inflammatory and anti-tumoural properties (Ulbricht et al., 2012). Machado et al. (2016) evaluated the therapeutic potential of açai extract (AE) on the growth of endometriotic lesions in rats. They found that AE significantly induces the regression and decreases the size of endometriotic lesions. Moreover, the treated lesions exhibited reduced levels of VEGF, MMP-9, COX-2, PGE_2 and nitric oxide when compared to controls (Machado et al., 2016).

Viburnum opulus extract

Viburnum opulus, also called European cranberry bush or guelder rose, is widespread in Europe, North and Central Asia as well as North Africa. The *V. opulus* fruits are used as food plant, herbal teas and medicinal plant to treat a wide range of illnesses (Polka et al., 2019). In animal studies, *Viburnum opulus* extract (VOE) protected the male reproductive system from damage caused by taxanes (Sarıözkan et al., 2017). In addition, it was found that daily oral treatment with VOE significantly reduces the volume of endometriotic lesions in rats (Saltan et al., 2016). Moreover, VOE-treated animals exhibited significantly lower peritoneal levels of TNF-α, VEGF and interleukin (IL)-6. Of note, these effects may be partially attributed to the chlorogenic acid compound of VOE (Saltan et al., 2016).

Silymarin extract

Milk thistle (*Silybum marianum*) is a medicinal plant from the Asteraceae family native in Southern Europe, Australia, North and South America, Northern Africa and some parts of Asia. Milk thistle has been used since ancient times for the treatment of liver diseases and for increasing milk production in lactating mothers (Soleimani et al., 2019). Silymarin extract (SE), the major constituent of milk thistle, is a mixture of flavonolignan and flavonoid polyphenolic compounds isolated from *S. marianum*, widely known for its potent anti-oxidant, anti-inflammatory, anti-proliferative and pro-apoptotic effects (Di Costanzo and Angelico, 2019). Accordingly, SE has been proposed as an anti-cancer and anti-metastatic natural compound (Hosseinabadi et al., 2019). In rats with surgically induced endometriosis, the total serum anti-oxidant activity was significantly higher in SE-treated animals when compared to controls (Jouhari et al., 2018). Two recent studies further demonstrated that SE induces the regression of endometriotic lesions in a rat model (Jouhari et al., 2018; Nahari and Razi, 2018). Additional molecular and histopathological analyses revealed an up-regulation of ERK1/2 expression and inhibition of angiogenesis, resulting in increased apoptosis and fibrosis within SE-treated endometriotic lesions (Nahari and Razi, 2018). Nevertheless, more studies are necessary to clarify whether SE is also appropriate for the treatment of human endometriosis. Clinical trials indicate that SE is safe in humans at therapeutic doses and well tolerated even at a high dose (>1500 mg/day) (Soleimani et al., 2019). However, the compound exhibits low solubility in water, low bioavailability and poor intestinal absorption. Therefore to improve its bioavailability at the site of absorption, the use of nanotechnology appears to be a promising method, allowing a sustained release and increased the therapeutic action of the active herbal extract (Di Costanzo and Angelico, 2019).

Calligonum comosum extract

Calligonum comosum is a leafless perennial shrub widespread in sand dunes. It grows naturally in the North African deserts, the desert sands of the Middle East, Pakistan and both Central and Eastern Arabia (Soliman et al., 2018). *Calligonum comosum* is useful in traditional folkloric medicine for the treatment of abnormally heavy or prolonged menstruation (Tahmasebi et al., 2018) and exhibits anti-

Table I Medicinal plants and herbal extracts evaluated in experimental models of endometriosis.

Herbal medicine	Model	Action/mechanism	Reference
Pueraria flower extract	Human endometriotic cell lines (11Z and 12Z)	↓ Cell migration and adhesion ↓MMP-2 and MMP-9 levels	Kim *et al.* (2017)
	Balb/c mice	↓ Endometriotic lesion size	Kim *et al.* (2017)
Hexane extract of aged black garlic	Primary human endometriotic stromal cells isolated from patients with ovarian endometrioma	↓ Cell proliferation ↓ Cell cycle progression ↓ ERK and JNK pathways ↓ TNF-α-induced ICAM-1 and VCAM-1 expression by inhibiting the activation of NF-κB and AP-1	Kim *et al.* (2013)
Uncaria tomentosa extract	Wistar rats	↓ Endometriotic lesion size	Neto *et al.* (2011)
Açai extract	Sprague-Dawley rats	↓ Endometriotic lesion size ↓ VEGF, MMP-9 and COX-2 ↓ PGE_2, VEGF and NO levels	Machado *et al.* (2016)
Viburnum opulus extract	Sprague-Dawley rats	↓ Endometriotic lesion size ↓ TNF-α, VEGF and IL-6 levels	Saltan *et al.* (2016)
Silymarin extract	Wistar rats	↓ Endometriotic lesion size	Jouhari *et al.* (2018)
	Wistar rats	↓ Endometriotic lesion size ↑ ERK1/2 expression ↓ Angiogenesis ↑ Apoptosis ↑ Fibrosis	Nahari and Razi (2018)
Calligonum comosum extract	Balb/c mice	↓ Endometriotic lesion size ↓ Vascularisation ↓ Cell proliferation ↓ Immune cell infiltration	Kiani *et al.* (2019)

AP-1, nuclear activator protein-l; COX-2, cyclooxygenase-2; ICAM-1, intercellular adhesion molecule-1; IL-6, interleukin-6; MMP, matrix metalloproteinase; NF-κB, nuclear factor-kappa B; NO, nitric oxide; PGE_2, prostaglandin E_2; PGF_2-α, prostaglandin F_2-α; TNF-α, tumour necrosis factor-α; VCAM-1, vascular cell adhesion molecule-1; VEGF, vascular endothelial growth factor.

inflammatory, anti-oxidant and anti-cancer activity (Badria *et al.*, 2007; Abdel-Sattar *et al.*, 2014; Abdo *et al.*, 2015). Recent findings indicate that *Calligonum comosum* extract (CCE) may also be beneficial for the treatment of endometriosis. After administration of CCE to mice with surgically induced endometriosis, an inhibition of growth and cyst formation of developing endometriotic lesions was observed. This was associated with reduced vascularisation, cell proliferation and immune cell infiltration within the lesions (Kiani *et al.*, 2019).

Summary

As summarised in Table I, the findings of the aforementioned basic studies indicate that several herbal extracts show potential for future use in endometriosis therapy. This is most probably due to their broad action profile, which includes anti-proliferative, anti-oxidant, anti-inflammatory, anti-angiogenic and pro-apoptotic activity. Future studies have to clarify now whether these beneficial effects observed under experimental conditions are also reproducible in endometriosis patients. For this purpose, it will be necessary to establish standardised protocols for the good manufacturing practice (GMP)-compliant generation of well-defined plant extracts. This is a major prerequisite for the systematic evaluation of their efficiency and safety in human endometriosis therapy.

Specific Plant-derived Bioactive Compounds

Specific plant-derived bioactive compounds with evidence about their inhibitory activity on endometriosis include resveratrol, epigallocatechin-3-gallate (EGCG), curcumin, puerarin, ginsenosides, xanthohumol, 4-hydroxybenzyl alcohol (4-HBA), quercetin, apigenin, carnosic acid, rosmarinic acid, wogonin, baicalein, parthenolide, andrographolide and cannabinoids (Fig. 1).

Resveratrol

Resveratrol is a natural phytoalexin polyphenol synthesised by plants for the protection against fungal infections. High resveratrol levels are detected in grapes, wine, berries and nuts (Rauf *et al.*, 2018; Dull *et al.*, 2019). Besides its cardioprotective effects, resveratrol exhibits anti-cancer properties, as indicated by its ability to suppress the proliferation of a wide variety of tumour cells (Kundu and Surh, 2008). In addition, resveratrol exhibits an anti-oxidant, anti-inflammatory and anti-angiogenic activity (Kundu and Surh, 2008; Dull *et al.*, 2019).

Several *in vitro* studies have analysed the effect of resveratrol on endometrial and endometriotic cells (Fig. 2). Bruner-Tran *et al.* (2011) demonstrated that resveratrol dose-dependently suppresses the invasiveness of human endometrial stromal cells into Matrigel®

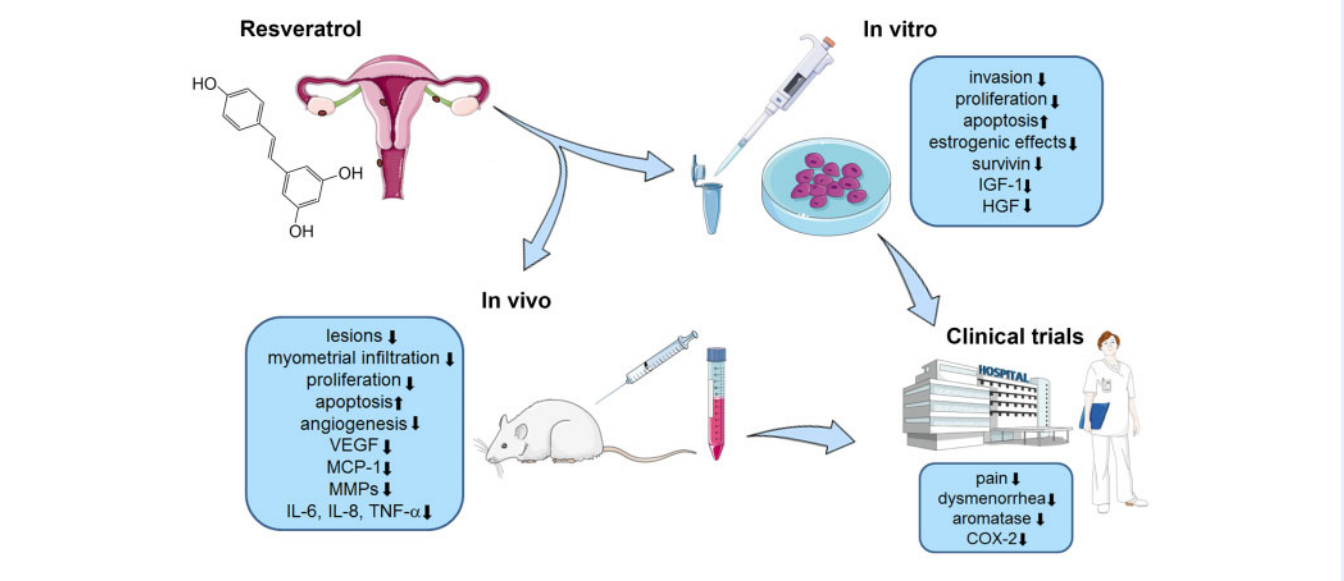

Figure 2. Resveratrol as a potential therapeutic in endometriosis. Preclinical *in vitro* studies on the polyphenol resveratrol have demonstrated an inhibitory effect on invasive growth and cell proliferation as well as a pro-apoptotic function. These effects can be partially attributed to an inhibitory effect on the expression of survivin, IGF-1 and HGF, while its effects on oestrogen are more complex. *In vivo* models of endometriosis confirm the anti-invasive and pro-apoptotic role as well as an inhibitory impact on angiogenesis, which is linked to a reduction in the expression of pro-inflammatory, pro-angiogenic and pro-invasive factors. A limited number of small clinical trials on the combination of oral contraceptives with resveratrol have revealed possible positive effects with respect to pain relief and decreased dysmenorrhea, however, one clinical trial failed to demonstrate positive effects. See text for details.

(Bruner-Tran *et al.*, 2011). Moreover, it inhibits cell proliferation and induces apoptosis in primary epithelial endometrial cell cultures from endometriosis and control women (Ricci *et al.*, 2013). Taguchi *et al.* (2016) found that resveratrol suppresses survivin expression and enhances tumour necrosis factor-related apoptosis-inducing ligand-induced apoptosis in endometriotic stromal cells from ovarian endometriosis (Taguchi *et al.*, 2016). *In vitro* effects of resveratrol have also been studied by Amaya *et al.* (2014) using the Ishikawa endometrial cell line. They reported that resveratrol alone has a weak oestrogen activity while in the presence of the steroid hormone it can act as either an oestrogen agonist or antagonist at low and high concentrations, respectively. Moreover, resveratrol may reduce endometrial cell proliferation through ER-α (Amaya *et al.*, 2014). Another study recently showed that resveratrol treatment of eutopic and ectopic endometrial stromal cells from endometriosis patients reduces their expression of insulin-like growth factor-1 (IGF-1) and hepatocyte growth factor (HGF), both important factors involved in the growth, proliferation and angiogenesis of endometriotic lesions (Arablou *et al.*, 2019).

In line with these promising *in vitro* results, several *in vivo* studies reported beneficial effects of resveratrol on endometriotic lesions in mice (Fig. 2). In a first report, human endometrial tissue was injected into the peritoneal cavity of oestrogen-stimulated nude mice, which either received resveratrol or vehicle by daily gavage (Bruner-Tran *et al.*, 2011). Resveratrol treatment reduced the fraction of animals developing endometriosis and the number of lesions as well as their total volume per mouse. In addition, resveratrol-treated lesions exhibited an increased apoptotic activity. Of note, these effects were observed at rather high resveratrol doses of 6 mg/mouse, which are not reasonable for human administration (Bruner-Tran *et al.*, 2011). Even higher doses of 60 mg/mouse were used in another immunocompromised murine model of endometriosis (Amaya *et al.*, 2014), reporting an anti-oestrogenic and anti-proliferative effect of the compound on human endometrial xenografts. However, beneficial effects on experimental endometriosis have also been induced in mice by applying markedly lower resveratrol doses ranging between 10 and 40 mg/kg per day (Ricci *et al.*, 2013; Rudzitis-Auth *et al.*, 2013). These effects included the suppression of cell proliferation and angiogenesis as well as the stimulation of apoptosis, resulting in a reduced engraftment and growth of endometriotic lesions (Ricci *et al.*, 2013; Rudzitis-Auth *et al.*, 2013).

In a rat model of endometriosis, Ergenoğlu *et al.* (2013) reported a significant reduction in implant size and considerable histological changes in endometriotic foci following a 14-day treatment with 10 mg/kg i.m. resveratrol. This was associated with decreased levels of VEGF and monocyte chemoattractant protein (MCP)-1 in the peritoneal fluid of the animals (Ergenoğlu *et al.*, 2013). In a similar model, Cenksoy *et al.* (2015) observed a regression of endometriotic lesions and lower VEGF and MCP-1 levels after a 21-day oral administration of resveratrol in a dose of 60 mg/kg. Of interest, they further compared the therapeutic efficiency of resveratrol with conventional GnRHa treatment and found that resveratrol was as effective as leuprolide acetate (Cenksoy *et al.*, 2015). Yavuz *et al.* (2014) treated rats with intraperitoneal doses of 1 or 10 mg/kg/day resveratrol, resulting in reduced cell proliferation rates and endometriotic implant volumes. Moreover, the activities of superoxide dismutase and glutathione peroxidase as well as the levels of malonyl dialdehyde and catalase increased in the serum

and tissue of the animals when compared to controls. Based on these data, the authors suggested that resveratrol suppresses the development of surgically induced rat endometriotic implants probably due to its anti-oxidative properties (Yavuz *et al.*, 2014). In addition, Bayoglu Tekin *et al.* (2015) showed that resveratrol is a potent inhibitor of endometriosis-associated inflammation and angiogenesis. They detected reduced levels of the pro-inflammatory cytokines IL-6, IL-8 and TNF-α in the peritoneal fluid of resveratrol-treated rats and a lower expression of MMPs and VEGF in endometriotic implants when compared to controls (Bayoglu Tekin *et al.*, 2015).

Although resveratrol is the most extensively studied stilbene and various preclinical studies indicate its effectiveness in the treatment of endometriosis, clinical endometriosis trials with resveratrol are limited. Maia *et al.* (2012) conducted a clinical study including 42 women with endometriosis. Of these, 16 patients received oral contraceptives alone, whereas 26 patients were treated with a combination of oral contraceptives and resveratrol. It was found that the expression of aromatase and COX-2 was reduced in the eutopic endometrium of patients treated with combined therapy when compared to the control group (Maia *et al.*, 2012). An additional study of the same authors conducted in 12 patients with endometriosis, who had failed to obtain pain relief during the use of combined oral contraceptives, further reported a clinical benefit of resveratrol. The addition of 30 mg resveratrol to their daily oral contraceptive regimen caused a significant reduction in pain scores, with 82% of patients reporting complete resolution of dysmenorrhea and pelvic pain after 2 months of therapy (Maia *et al.*, 2012). Taken together, these results indicate that resveratrol potentiates the effects of oral contraceptives in the management of endometriosis-associated dysmenorrhea, by further reducing aromatase and COX-2 expression in the endometrium, although this should be confirmed in larger trials (Fig. 2). More recently, Mendes da Silva *et al.* (2017) conducted a randomised clinical trial involving 44 women with laparoscopic diagnosis of endometriosis to evaluate the effectiveness of resveratrol in the management of endometriosis associated with monophasic contraceptive pills. However, they found that the dose of 40 mg/day resveratrol did not improve endometriosis-related symptoms when compared to placebo-treated controls (Mendes da Silva *et al.*, 2017).

Epigallocatechin-3-gallate

EGCG is a flavonoid found both in black, but especially in green tea. In recent years, the compound has been considered for the treatment of different types of cancer based on its anti-oxidant, anti-angiogenic and anti-proliferative effects (Ju *et al.*, 2007; Shanmugam *et al.*, 2011; Singh *et al.*, 2015). The first study evaluating the effect of EGCG in the treatment of experimental endometriosis was performed in Syrian golden hamsters (Laschke *et al.*, 2008). EGCG suppressed the proliferation and VEGF expression of isolated hamster endometrial stromal and glandular cells. *In vivo*, EGCG inhibited angiogenesis, blood perfusion and growth of endometriotic lesions within dorsal skinfold chambers (Laschke *et al.*, 2008). Xu *et al.* (2009) subcutaneously transplanted eutopic endometrium from patients with endometriosis into immunodeficient mice, which were intraperitoneally treated with EGCG for 2 weeks. This treatment significantly suppressed the development of endometriotic lesions by inhibition of angiogenesis, as indicated by a decreased microvessel density and reduced mRNA levels of VEGF within the lesions. In addition, the lesions contained higher numbers of apoptotic cells when compared to controls (Xu *et al.*, 2009). In a follow-up study, Xu *et al.* (2011) further reported that EGCG selectively suppresses VEGFC/VEGF receptor-2 (VEGFR-2) expression and signalling in experimental endometriosis *in vivo* and in endothelial cells *in vitro* (Xu *et al.*, 2011). In addition, they evaluated a prodrug of EGCG (pro-EGCG, EGCG octaacetate) with improved stability and bioavailability (Wang *et al.*, 2013). This prodrug exhibited a stronger anti-oxidant activity than EGCG and, thus, represents a promising compound for endometriosis therapy (Wang *et al.*, 2013). Ricci *et al.* (2013) were the first demonstrating the effectiveness of oral EGCG administration in a murine model of endometriosis. They showed that oral gavage of EGCG for 4 weeks inhibits the development of endometriotic lesions by diminishing cell proliferation and increasing apoptosis. Moreover, EGCG treatment reduced the number of established lesions per mouse (Ricci *et al.*, 2013). Using epithelial endometrial cells from human biopsies, it was further shown that EGCG also suppresses cell proliferation and induces cell death in cells of human origin (Ricci *et al.*, 2013). A more recent study revealed that EGCG inhibits cell proliferation, migration, invasion and collagen gel contraction of endometrial and endometriotic stromal cells *in vitro* (Matsuzaki and Darcha, 2014). This was associated with a significantly decreased expression of genes known to be involved in fibrogenesis. Interestingly, the anti-proliferative effect of EGCG was significantly more pronounced in endometriotic stromal cells than in endometrial stromal cells from patients with endometriosis. These findings are in accordance with other studies observing that EGCG more strongly suppresses cell proliferation of diseased cells than of their normal cell counterparts (Chen *et al.*, 2011a). Moreover, it was shown that EGCG prevents the progression of fibrosis within endometriotic lesions in a xenograft model (Matsuzaki and Darcha, 2014).

Of interest, the Chinese University of Hong Kong is currently recruiting for a randomised interventional clinical trial on 185 prospective endometrioma patients, who will be given high-purity EGCG (SUNPHENON EGCg®; 400 mg, twice per day) or a placebo for 3 months prior to their planned surgery. Change in endometriotic lesion size (by MRI) is listed as a primary outcome, whereas pain scores, quality of life, change in lesion growth (by biopsy), change in neovascularisation and monitoring of adverse effects are listed as secondary outcomes (Wang, 2020a).

Curcumin

Curcumin is a polyphenolic compound found in turmeric, which is derived from the rhizomes of the plant Curcuma longa Linn (Bisht *et al.*, 2010). The anti-inflammatory and cytoprotective properties of curcumin have been widely reported (Bisht *et al.*, 2010; Kim *et al.*, 2012). The anti-inflammatory effect of curcumin on endometriosis was investigated by Kim *et al.* (2012) using primary endometriotic stromal cells obtained from ovarian endometrioma. They observed that this compound suppresses ICAM-1 and VCAM-1 gene and protein expression as well as the secretion of IL-6, IL-8 and MCP-1 by inhibiting the TNF-α-induced activation of NF-κB. However, it had no significant effect on the viability of human endometriotic stromal cells (Kim *et al.*, 2012). In another *in vitro* study, Zhang *et al.* (2013a) found that curcumin is able to inhibit the proliferation of endometrial cells by reducing E_2 levels (Zhang *et al.*, 2013a). Moreover, Cao *et al.* (2017a) observed in cell

cycle analyses that curcumin increases the percentage of G1 phase cells in human endometriotic stromal cells, whereas the percentage of S phase cells and expression of VEGF is decreased. Hence, curcumin seems to reduce cell proliferation in human endometriotic stromal cells via down-regulation of the VEGF signalling pathway (Cao et al., 2017a). Recently, Chowdhury et al. (2019) detected a reduced secretion of different pro-angiogenic chemokines and pro-inflammatory cytokines from normal endometrial stromal cells and from eutopic endometrium of endometriosis subjects treated with curcumin. In contrast, the anti-inflammatory cytokines IL-10 and IL-12 were up-regulated by curcumin, particularly in endometrial stromal cells derived from endometriosis patients (Chowdhury et al., 2019). This indicates that the beneficial effects of curcumin on endometriosis may be mediated by an imbalance between pro- and anti-inflammatory factors.

In vivo, such beneficial curcumin effects have been reported by several groups in rat models of the disease (Yun-Fei et al., 2012; Kizilay et al., 2017; Jelodar and Azimifar, 2019). Yun-Fei et al. (2012) demonstrated that 150 mg/kg/day of intragastrically administered curcumin for three continuous weeks significantly reduces the volume and weight of endometriotic lesions. Because this was associated with a lower microvessel density within the lesions, they suggested that curcumin may inhibit the development of endometriosis by suppression of angiogenesis (Yun-Fei et al., 2012). This view is supported by another study of Zhang et al. (2011) demonstrating that curcumin doses of 50–150 mg/kg/day inhibit blood vessel formation in rat endometriotic lesions by down-regulating VEGF expression (Zhang et al., 2011).

In murine endometriotic lesions, curcumin has been shown to inhibit NF-κB translocation as well as expression of MMP-2 and MMP-3 (Jana et al., 2012). Moreover, it stimulates apoptosis via the cytochrome-c-mediated mitochondrial pathway (Jana et al., 2012). In another study, 40 mg/kg/day curcumin encapsulated in poly(lactic-co-glycolic acid) nanoparticles suppressed oxidative stress parameters, angiogenic markers, matrix degrading molecules, oestrogen levels, endometriotic lesion size and microvessel density in the peritoneum of mice (Jana et al., 2014). In addition, Swarnakar and Paul (2009) reported that curcumin administered either pre- or post-induction of endometriosis inhibits the development of murine endometriotic lesions and reduces MMP-9 activity. Moreover, pretreatment with curcumin prevented lipid peroxidation and protein oxidation (Swarnakar and Paul, 2009). Hence, curcumin is a typical pleiotropic compound, which targets multiple molecular and cellular mechanisms in the pathogenesis of endometriosis (Arablou and Kolahdouz-Mohammadi, 2018).

Currently, the Vienna-based ENDOFLEX study is recruiting endometriosis patients for a randomised interventional clinical trial on placebo versus the dietary supplement flexofytol, with planned administration of two capsules containing 42 mg of curcumin twice a day for a duration of 4 months in the verum group. The study defines a possible change in the average pain score, from baseline to 4 months after the onset of treatment, as primary outcome, and changes in the number of days with pain, alleviation of dyspareunia, dysuria and dyschezia as well as changes in quality of life and sexual function as secondary outcomes (Perricos, 2020).

Puerarin

Puerarin is the main component of the root of *P. lobata*. This medicinal plant has a long history in China and possesses a wide range of pharmacological properties (Zhang, 2019). The effects of puerarin on aromatase P450 (P450arom) expression in Ishikawa and RL95-2 endometrial carcinoma cell lines were assessed by Li et al. (2008). They demonstrated a significant decrease in P450arom expression at both mRNA and protein levels provoked by low-dose puerarin treatment in both cell lines (Li et al., 2008). In addition, puerarin suppressed E_2-induced proliferation of endometriotic stromal cells partly via down-regulation of a non-genomic membrane-initiated ERK pathway and inhibition of cyclin D1, COX-2 and Cyp19 gene expression (Cheng et al., 2012). Moreover, puerarin inhibited the invasion of endometriotic stromal cells and the vascularisation of ectopic endometrial tissues in the chicken chorioallantoic membrane model (Wang et al., 2011). This was associated with a reduced cellular accumulation of MMP-9, ICAM-1 and VEGF, whereas the expression of tissue inhibitors of metalloproteinases (TIMP)-1 increased after puerarin treatment (Wang et al., 2011). Ji et al. (2013) showed that puerarin suppresses the oestrogen-stimulated proliferation of endometriotic stromal cells partly through down-regulating the transcription of cyclin D1 and cdc25A (Ji et al., 2013).

In addition to these *in vitro* results, two studies also analysed the effect of puerarin in animal models of endometriosis. Chen et al. (2011b) orally administered the compound at three different doses, i.e. 60, 200 or 600 mg/kg/day, to rats, in which endometriotic lesions were successfully induced by transplanting autologous endometrial tissue to ectopic sites (Chen et al., 2011b). Even the lowest dose significantly reduced the weight of endometriotic tissue and serum oestrogen levels without adverse effects. Yu et al. (2015) demonstrated that puerarin inhibits the growth of rat endometriotic lesions due to the inhibition of P450arom and COX-2 expression. Puerarin further reduced the levels of E_2 and PGE_2 and blocked the positive feedback mechanism of E_2 synthesis by up-regulating the expression of 17β-hydroxysteroid dehydrogenase-2 (17β-hsd-2) and down-regulating the expression of 17β-hydroxysteroid dehydrogenase-1 (17β-hsd-1) (Yu et al., 2015).

Ginsenosides

Pharmacologic studies have shown that most of the biological activities of ginseng, the root of Panax ginseng, are derived from its main components, the ginsenosides (Dong-Soon and Seung-Yeol, 2013). A number of studies have reported that ginsenosides (e.g. ginsenoside-Rg3 and ginsenoside Rh2) and their metabolites (protopanaxadiol, PPD and protopanaxatriol, PPT) exhibit anti-tumour, anti-oxidant, immunomodulatory and anti-inflammatory activities (Zhang et al., 2018). Huang et al. (2020) recently exposed endometriotic stromal cells from patients with ovarian endometriosis to Rg3, which inhibited their proliferation in a time- and dose-dependent manner. In addition, Rg3 treatment significantly diminished the activity of NF-κB, up-regulated the expression of caspase-3 and suppressed the expression of VEGF (Huang et al., 2020). In another study, Rg3 inhibited the development of endometriotic lesions in rats, which were induced by allotransplantation of endometrial tissue. The authors suggested that this effect is mediated by blockade of the VEGFR-2-activated PI3K/Akt/mTOR signalling pathway (Cao et al., 2017b). Qin et al., (2019) found that treatment with the ginsenoside Rf decreases the volume of endometriotic lesions and reduces the expression levels of VEGF and inflammation-related cytokines in rats. Of interest, they also showed that Rf inhibits

the expression of brain-derived neurotrophic factor, which could be involved in the alleviation of endometriosis-associated pain (Qin *et al.*, 2019). Zhang *et al.* (2018) observed that PPD, PPT, Rg3, Rh2 and esculentoside-A affect viability of, and induce autophagy in ectopic endometrial stromal cells. In addition, all compounds decreased the number and suppressed the growth of ectopic lesions in a murine endometriosis model (Zhang *et al.*, 2018).

Xanthohumol

Numerous studies have demonstrated the broad anti-cancer and anti-metastatic activities of xanthohumol, a flavonoid isolated from hops (*Humulus lupulus* L.), owing to its anti-proliferative, anti-inflammatory and anti-angiogenic properties (Jiang *et al.*, 2018). Accordingly, 100 μM xanthohumol administered in the drinking water of mice with surgically induced endometriosis inhibited the development of endometriotic lesions independently of their localisation within the peritoneal cavity (Rudzitis-Auth *et al.*, 2012). Moreover, xanthohumol suppressed angiogenesis and cell proliferation within the lesions (Rudzitis-Auth *et al.*, 2012). Of interest, it was further found that treatment with xanthohumol did not affect the histomorphology, proliferation and vascularisation of the uterine horns and ovaries, suggesting that the treatment with this flavonoid may not induce side effects within the reproductive organs when treating endometriosis (Rudzitis-Auth *et al.*, 2012).

4-Hydroxybenzyl alcohol

4-HBA, one of the major active phenolic constituents of *Gastrodia elata* Blume, is an effective agent against several central and peripheral nervous disorders (Yu *et al.*, 2010). This phenolic compound exerts antioxidant, anti-inflammatory and anti-angiogenic actions on several experimental tumour models (Park *et al.*, 2010; Laschke *et al.*, 2013). Moreover, 4-HBA has been reported to inhibit the proliferation and migration of murine endothelial-like eEND2 cells, which is associated with a reduced expression of VEGF and MMP-9 (Laschke *et al.*, 2011). *In vivo*, 4-HBA suppressed the vascularisation and growth of developing endometriotic lesions in the dorsal skinfold chamber model (Laschke *et al.*, 2011).

Quercetin

Quercetin is ubiquitously present in fruits and vegetables, and is therefore one of the most common dietary flavonols in the Western diet. The anti-cancer effects of quercetin include its ability to reduce cell viability and increase apoptosis and autophagy through the modulation of PI3K/Akt/mTOR, Wnt/β-catenin and MAPK/ERK1/2 pathways (Reyes-Farias and Carrasco-Pozo, 2019). In rats with surgically induced endometriosis, quercetin inhibited the growth of endometriotic lesions through decreasing serum FSH and LH levels as well as reducing the local oestrogen content. Quercetin also decreased the expression of ER-α, ER-β and progesterone receptor in the hypothalamus, pituitary and endometrium, thereby inhibiting oestrogen and progesterone binding to their receptors (Cao *et al.*, 2014). In addition, Park *et al.* (2019) showed that quercetin inhibits cell proliferation and induces cell cycle arrest and apoptosis of the endocervical cell lines VK2/E6E7 and End1/E6E7. This was associated with the down-regulation of ERK1/2, P38 MAPK and AKT signalling molecules. Moreover, the intraperitoneal administration of quercetin in a mouse model of endometriosis decreased the size of endometriotic lesions and exerted anti-proliferative and anti-inflammatory effects when compared to vehicle treatment in mice (Park *et al.*, 2019).

Apigenin

Apigenin is a natural bioactive flavonoid present in significant amounts within vegetables (parsley, celery, onions), fruits (oranges), herbs (chamomile, thyme, oregano, basil) and plant-based beverages (tea, beer, wine), which has been suggested to be suitable for the prevention and treatment of cancer, diabetes and Alzheimer's disease (Salehi *et al.*, 2019). Apigenin exerts anti-proliferative, anti-inflammatory and anti-angiogenic effects in cancer and metabolic diseases and, thus, has also been proposed as a potential therapeutic agent for endometriosis. In this context, apigenin has been shown to attenuate TNF-α-induced cell proliferation as well as COX-2 and PGE_2 synthesis via the inactivation of the NF-κB pathway in endometriotic stromal cells isolated from human endometriomas (Suou *et al.*, 2011). Moreover, Park *et al.* (2018) found that apigenin induces apoptosis in two human endometriotic cell lines through inhibition of phosphorylation of JNK and ERK1/2. Apigenin also reduced cell proliferation and induced cell cycle arrest in the two cell lines. However, the efficiency of the compound has not been evaluated so far in preclinical animal models of endometriosis (Park *et al.*, 2018).

Carnosic acid and rosmarinic acid

The phenolic diterpene, carnosic acid, and the polyphenol, rosmarinic acid, are the most abundant active compounds in rosemary leaves (*Rosmarinus officinalis*) and are thus responsible for the anti-oxidant activity of this plant (Moore *et al.*, 2016). Their anti-cancer (López-Jiménez *et al.*, 2013; Moore *et al.*, 2016) and anti-inflammatory effects (Yesil-Celiktas *et al.*, 2010; Petiwala and Johnson, 2015) have been demonstrated by several studies. Ferella *et al.* (2018) evaluated the effect of carnosic acid and rosmarinic acid on the development of experimental endometriosis. *In vitro*, carnosic acid and rosmarinic acid significantly inhibited cell proliferation in primary cultures and a human endometrial stromal cell line (T-HESC). Moreover, a strong antioxidant effect was observed after the exposure of T-HESC to rosmarinic acid, suggesting a possible role for reactive oxygen species (ROS) in the regulation of cell proliferation. *In vivo*, carnosic acid and rosmarinic acid significantly reduced the size of surgically induced endometriotic lesions in mice when compared to controls. Both compounds significantly suppressed cell proliferation, whereas rosmarinic acid additionally promoted apoptotic cell death within the lesions (Ferella *et al.*, 2018).

Wogonin and baicalein

Wogonin and baicalein are the main flavonoids isolated from the root of *Scutellaria baicalensis* (Li-Weber, 2009; Lee *et al.*, 2014). Their antitumour, anti-proliferative, anti-inflammatory and pro-apoptotic properties have already been demonstrated in different studies (Li-Weber, 2009; Wu *et al.*, 2016). Recent results provide evidence of an anti-proliferative effect of wogonin on human endometrial stromal cells, caused by the induction of cell cycle arrest at the G2/M phase (Ferella *et al.*, 2018). The inhibitory action of this flavonoid on the growth of

endometriotic lesions has been further demonstrated in a murine endometriosis model (Ferella et al., 2018). In addition, it was observed that baicalein significantly reduces the viability of human endometriotic stromal cells in culture, provokes G1 phase cell cycle and reduces the expression of the anti-apoptosis protein Bcl-2. The latter finding indicates that baicalein may induce apoptosis in human endometrial stromal cells (Jin et al., 2017).

Parthenolide

Parthenolide, a main active component of the traditional medical plant feverfew (*Tanacetum parthenium*), exhibits potent anti-cancer activities (Ghantous et al., 2013). In particular, parthenolide exerts anti-inflammatory, redox-modulating and epigenetic effects as well as selective cytotoxicity towards cancer stem and progenitor cells (Freund et al., 2020). In experimental studies, parthenolide inhibited the NF-κB pathway and suppressed TNF-α-induced PGE_2 and DNA synthesis in endometrial stromal cells isolated from human endometriomas (Takai et al., 2013). In line with these findings, parthenolide further inhibited the formation of murine endometriotic lesions and the expression of pro-inflammatory-associated genes in a BALB/c mouse model of endometriosis (Takai et al., 2013).

Andrographolide

Andrographolide is the main active constituent present in *Andrographis paniculata*, a medicinal plant that has been widely used in complementary medicine, especially in Southeast Asia, China and India. Andrographolide has anti-thrombotic, anti-cancer and anti-inflammatory properties (Tan et al., 2017; Soo et al., 2019). Accordingly, andrographolide has been shown to inhibit cell cycle progression and cell proliferation through inhibition of the NF-κB pathway and to inhibit COX-2 and tissue factor expression in primary cell cultures of endometriotic stromal cells. In addition, andrographolide-treated endometriotic lesions in rats exhibited a reduced size and expression of active NF-κB subunits, nerve growth factor and COX-2. This was associated with a reduced pain behaviour of the treated animals, indicating that the compound is a potential anti-inflammatory and analgesic candidate for the treatment of endometriosis (Zheng et al., 2012).

Cannabinoids

Particularly in pain-associated pathologies, there is an increasing interest in the use of cannabis-based medicines. They contain cannabinoids derived from the cannabis plant, including delta-9-tetrahydrocannabinol (THC), the main psychoactive constituent of the Cannabis sativa plant, cannabidiol (CBD) or a combination of both (Boyaji et al., 2020). Two kinds of cannabinoid receptors are described: the cannabinoid 1 (CB1) and 2 (CB2) receptors. CB1 receptors are highly expressed in the uterus as well as in the spleen, heart, adrenal gland, ovaries and testes, among other tissues. The CB2 receptors are preferentially expressed in the immune system and intestine (Walker et al., 2019).

Some of the studies recently reviewed by Bouaziz et al. (2017) described endometriosis as an 'endocannabinoid deficiency' condition. It was reported that women with endometriosis have lower levels of CB1 receptors in their endometrial tissue (Bouaziz et al., 2017). Hence, the endocannabinoid system (ECS) could be important for the establishment of pain associated with endometriosis, because reduced ECS function has been suggested to promote a more severe pain experience (Bouaziz et al., 2017).

The effects of subcutaneous administration of THC in a mouse model of surgically induced endometriosis were evaluated by Escudero-Lara et al. (2020). In this work, female mice, which develop mechanical hypersensitivity in the caudal abdomen, mild anxiety-like behaviour and substantial memory deficits associated with the presence of experimental endometriosis, were treated daily with THC (2 mg/kg). Interestingly, a moderate dose of the phytocannabinoid was effective in alleviating mechanical hypersensitivity and pain and restoring cognitive function without altering the anxiogenic phenotype. Strikingly, THC also inhibited the development of endometrial cysts (Escudero-Lara et al., 2020). These data highlight the interest of scheduled clinical trials designed to investigate possible benefits of THC for women with endometriosis. Regarding ongoing studies, the NIH-based database ClinicalTrials.gov only lists a currently recruiting phase 2 open label interventional clinical trial to study the effect of cannabinoid (THC/CBD 50%) on hyperalgesia in patients with deep endometriosis (Garcia Cinca, 2020), but no larger trials. It should be noted that targeting endocannabinoid modulation is probably even more than just treating pain, as it may also inhibit the growth of endometriotic tissue (Bouaziz et al., 2017). Hence, this type of phytotherapy has great potential for clinical use. Nonetheless, more investigation is needed to evaluate its efficiency and potential therapeutic side effects during chronic use, especially on fertility and pregnancy outcomes (Bouaziz et al., 2017).

Summary

As summarised in Table II, several specific plant-derived bioactive compounds have been shown to exert beneficial effects on endometriotic cells or lesions. In contrast to conventional drugs, they typically do not selectively inhibit one molecular target, but exhibit a pleiotropic action profile, which may simultaneously affect multiple signalling pathways. While this can markedly increase their efficacy in the treatment of endometriosis, it also complicates the identification of key mechanisms that mediate their therapeutic effects. Another important issue is the fact that most plant-derived bioactive compounds exhibit a low *in vivo* stability and bioavailability, which makes their efficient use in endometriosis patients difficult (Wieser et al., 2007). To overcome this problem, it will be necessary to identify analogues or to develop novel derivatives or prodrugs with improved pharmacokinetic properties. Moreover, sophisticated carrier systems are required, to selectively accumulate in endometriotic tissue, leading to high local compound concentrations without inducing systemic side effects. While challenging, these goals appear realistic considering the rapid progress in modern drug design and nanotechnology. Accordingly, the first promising steps towards this direction have already been taken for resveratrol, EGCG, quercetin, baicalein and curcumin (Davatgaran-Taghipour et al., 2017; Shi et al., 2018; Intagliata et al., 2019; Vinayak and Maurya, 2019). For instance, demethoxycurcumin, a naturally occurring curcumin analogue, which lacks the methoxy group on the benzene ring of the parent structure, exhibits a much higher chemical stability at physiological pH (Hatamipour et al., 2019). Hence, this curcuminoid has already been suggested for the treatment of different diseases, such as cancer, malaria, Parkinson's disease, rheumatoid arthritis, inflammatory bowel

Table II Plant-derived bioactive compounds evaluated in experimental models of endometriosis.

Bioactive compound	Model/dosage	Action/mechanism	Reference
Resveratrol	Primary human endometrial stromal cells	↓ Invasiveness	Bruner-Tran *et al.* (2011)
	Primary human endometrial epithelial cells	↓ Cell proliferation ↑ Apoptosis	Ricci *et al.* (2013)
	Primary human endometriotic stromal cells	↑ TRAIL-induced apoptosis ↓ Survivin	Taguchi *et al.* (2016)
	Primary human endometriotic stromal cells	↓ TNF-α-induced IL-8 release	Taguchi *et al.* (2014)
	Ishikawa epithelial endometrial cell line	↓ IGF-1 and HGF levels	Arablou *et al.* (2019)
	Heterologous model of endometriosis in nude mice (6 mg/mouse by gavage)	↓ Number of lesions ↓ Endometriotic lesion size ↑ Apoptosis	Bruner-Tran *et al.* (2011)
	Xenograft implants of human endometrial tissue in immunodeficient RAG-2-g(c) mice (6, 30 or 60 mg/day s.c.)	↓ Expression of ESR1 (with 60 mg/day) ↓ Proliferative activity (with 60 mg/day)	Amaya *et al.* (2014).
	Balb/c mice with induced endometriosis (10 or 25 mg/kg/day i.p.)	↓ Cell proliferation ↑ Apoptosis ↓ Number of lesions (with 25 mg/kg/day)	Ricci *et al.* (2013)
	Balb/c mice with induced endometriosis (40 mg/kg/day by gavage)	↓ Endometriotic lesion size ↓ Cell proliferation ↓ Angiogenesis	Rudzitis-Auth *et al.* (2013)
	Sprague-Dawley rats with induced endometriosis (10 mg/kg/day i.m.)	↓ Endometriotic lesion size ↓ VEGF levels ↓ MCP-1 levels	Ergenoğlu *et al.* (2013)
	Wistar rats with induced endometriosis (60 mg/kg/day by gavage)	↓ Histopathological scores of endometriotic lesions ↓ VEGF levels ↓ MCP-1 levels	Cenksoy *et al.* (2015)
	Wistar rats with induced endometriosis (1 or 10 mg/kg/day i.p.)	↓ Endometriotic lesion size ↓ Cell proliferation ↑ Superoxide dismutase and glutathione ↑ Malonyl dialdehyde and catalase	Yavuz *et al.* (2014)
	Sprague-Dawley rats with induced endometriosis (1 or 30 mg/kg/day i.m.)	↓ Endometriotic lesion size ↓ IL-6, IL-8 and TNF-α ↓ VEGF levels ↓ MMP-2 and MMP-9 expression	Bayoglu Tekin *et al.* (2015)
EGCG	Hamster endometrial glandular cells and endometrial stromal cells	↓ Cell proliferation ↓ VEGF levels	Laschke *et al.* (2008)
	Primary human endometrial epithelial cells	↓ Cell proliferation ↑ Apoptosis	Ricci *et al.* (2013)
	Primary human endometrial and endometriotic stromal cells	↓ Cell proliferation ↓ Invasion ↓ Migration ↓ Fibrotic markers ↓ TGF-β1-stimulated activation of MAPK and Smad	Matsuzaki and Darcha (2014)
	Endometrial fragments transplanted into the dorsal skinfold chamber of female Syrian golden hamsters (65 mg/kg/day i.p.)	↓ Endometriotic lesion size ↓ Angiogenesis	Laschke *et al.*, (2008)
	Heterologous immunocompromised mouse model of experimental endometriosis (50 mg/kg/day i.p.)	↓ Endometriotic lesion size ↑ Apoptosis ↓ Angiogenesis ↓ VEGF levels ↓ VEGFR-2 expression	Xu *et al.* (2009)
	Balb/c mice with induced endometriosis (20 or 100 mg/kg/day by gavage)	↓ Endometriotic lesion size ↓ Cell proliferation ↑ Apoptosis	Ricci *et al.* (2013)
	Heterologous model of endometriosis in nude mice (50 mg/kg/day i.p.)	↓ Fibrosis	Matsuzaki and Darcha (2014)

Continued

Table II Continued

Bioactive compound	Model/dosage	Action/mechanism	Reference
Curcumin	Human endometriotic stromal cells from ovarian endometrioma	↓ ICAM-1 and VCAM-1 expression ↓ IL-6, IL-8 and MCP-1 secretion ↓ Activation of NF-κB-induced by TNF-α	Kim et al. (2012)
	Human endometriotic cells and normal endometrial cells	↓ Cell proliferation ↓ E_2 levels	Zhang et al. (2013a)
	Human endometriotic stromal cells from endometriosis patients	↓ Cell proliferation ↑ Percentage of G1 phase cells ↓ Percentages of S phase cells ↓ VEGF levels	Cao et al. (2017a)
	Human endometriotic stromal cells from endometriosis patients	↓ Pro-inflammatory and pro-angiogenic chemokine and cytokine secretion ↑ IL-10 and IL-12 secretion	Chowdhury et al. (2019)
	Surgically induced endometriosis in rats (150 mg/kg/day by gavage)	↓ Endometriotic lesion size ↓ Microvessel density	Yun-Fei et al. (2012)
	Wistar rats with induced endometriosis (50, 100 or 150 mg/kg/day by gavage)	↓ Endometriotic lesion size ↓ Angiogenesis ↓ VEGF levels	Zhang et al. (2011)
	Wistar rats with induced endometriosis (100 mg/kg/day by gavage)	↓ Endometriotic lesion size ↓ Cell proliferation	Kizilay et al. (2017)
	Sprague-Dawley rats with induced endometriosis (48 mg/kg/day i.p.)	Suppression of the growth of endometriotic lesions	Jelodar and Azimifar (2019)
	Balb/c mice with induced endometriosis (protective effect: 16, 24 or 48 mg/kg i.p. 30 min prior the induction of endometriosis and once daily for the next 3 days; therapeutic effect: 48 mg/kg/day i.p for 10 days)	↓ Endometriotic lesion size ↑ Apoptosis ↓ NF-κB translocation ↓ MMP-3 expression	Jana et al. (2012)
	Swiss Albino mice with induced endometriosis (40 mg/kg/day encapsulated in PLGA nanoparticles)	↓ Endometriotic lesion size ↓ Oxidative stress parameters ↓ Angiogenesis ↓ Oestrogen levels	Jana et al. (2014)
	Balb/c mice with induced endometriosis (protective effect: 16, 32 or 48 mg/kg i.p. 30 min prior the induction of endometriosis and once daily for the next 3 days; therapeutic effect: 48 mg/kg/day i.p. for 10 days)	↓ Lipid peroxidation ↓ Protein oxidation ↓ MMP-9 activity	Swarnakar and Paul (2009)
Puerarin	Ishikawa and RL95 endometrial cell lines	↓ P450Arom expression and activity	Li et al. (2008)
	Human endometriotic stromal cells from ovarian endometrioma	↓ Cell proliferation ↓ Cyclin D1, Cox-2, Cyp19 expression	Cheng et al. (2012)
	Human endometriotic stromal cells from ovarian endometrioma	↓ Invasion ↓ Vascularisation ↓ MMP-9 ↓ ICAM ↓ VEGF ↑ TIMP-1	Wang et al. (2011)
	Human endometriotic stromal cells from ovarian endometrioma	↓ Cell proliferation ↓ Cyclin D1, cdc25A	Ji et al. (2013)
	Sprague-Dawley rats with induced endometriosis (60, 200 or 600 mg/kg/day by gavage)	↓ Endometriotic lesion size ↓ P450Arom expression ↓ E_2 levels	Chen et al. (2011b)
	Sprague-Dawley rats with induced endometriosis (5, 20 or 80 mg/kg/day i.p.)	↓ Endometriotic lesion size ↓ P450Arom ↓ COX-2 ↓ E_2 levels ↓ PGE_2 ↑ 17β-hsd-2 ↓ 17β-hsd-1	Yu et al. (2015)

Continued

Table II Continued

Bioactive compound	Model/dosage	Action/mechanism	Reference
Ginsenosides	Human endometriotic stromal cells from ovarian endometrioma Rg3	↓ Cell proliferation ↓ NF-κB activity ↓ VEGF ↑ Caspase-3	Huang *et al.* (2020)
	Human ectopic endometrial cells PPD, PPT, Rg3, Rh2 or EsA	↓ Cell proliferation ↑ Autophagy	Zhang *et al.* (2018)
	Sprague-Dawley rats with induced endometriosis (5 or 10 mg/kg/day of Rg3)	↓ Endometriotic lesion size ↓ VEGFR-2 mediated PI3K/Akt/mTOR signalling pathway	Cao *et al.* (2017b)
	Wistar rats with induced endometriosis (1, 2 or 4 mg/kg/day i.p. of Rf)	↓ Endometriotic lesion size ↓ VEGF ↓ iNOS ↓ IL-6 ↓ IL-1β ↓ TNF-α ↓ BDNF	Qin *et al.* (2019)
	Balb/c mice with induced endometriosis (45, 30 or 15 mg/kg of PPD, PPT, Rg3, Rh2 or EsA on day 4 and day 10, i.p.)	PPD, PPT, Rg3, Rh2 or EsA ↓ Endometriotic lesion size ↓ Number of lesions	Zhang *et al.* (2018)
Xanthohumol	Balb/c mice with induced endometriosis (100 μM xanthohumol via drinking water)	↓ Endometriotic lesion size ↓ PI3 kinase ↓ Angiogenesis ↓ Cell proliferation	Rudzitis-Auth *et al.* (2012)
4-HBA	Murine endothelial-like eEND2 cells	↓ Cell proliferation ↓ MMP-2 and VEGF ↓ Cell migration	Laschke *et al.* (2011)
	Endometrial fragments transplanted into the dorsal skinfold chamber of C57BL/6 mice (100 mg/kg/day i.p.)	↓ Endometriotic lesion size ↓ Angiogenesis	Laschke *et al.* (2011)
Quercetin	Sprague-Dawley rats with induced endometriosis (60, 150 or 375 mg/kg/day i.p.)	↓ Serum FSH and LH levels ↓ Serum oestrogen content ↓ ERα, ERβ and PR in hypothalamus, pituitary and endometrium	Cao *et al.* (2014)
	Endocervical cell lines VK2/E6E7 and End1/E6E7	↓ Cell proliferation ↓ ERK1/2, P38 MAPK and AKT ↑ Cell cycle arrest	Park *et al.* (2019)
	C57BL/6 mice with induced endometriosis (35 mg/kg/day i.p.)	↓ Endometriotic lesion size ↓ Cell proliferation ↓ Inflammation	Park *et al.* (2019)
Apigenin	VK2/E6E7 and End1/E6E7 endometriosis cell lines	↓ Cell proliferation ↑ Apoptosis ↑ Cell cycle arrest	Park *et al.* (2018)
	Human endometriotic stromal cells from ovarian endometrioma	↓ Cell proliferation ↓ IkB phosphorylation ↓ COX-2 ↓ PGE_2	Suou *et al.* (2011)
Carnosic acid and rosmarinic acid	Primary endometrial stromal cells from patients with endometriosis Human endometrial stromal cell line (T-HESC)	↓ Cell proliferation ↓ Oxidation	Ferella *et al.* (2018)
	Balb/c mice (CA 2mg/kg/day or 20mg/kg/day i.p) (RA 1mg/kg/day or 3mg/kg/day i.p)	↓ Endometriotic lesion size ↓ Cell proliferation ↑ Apoptosis	Ferella *et al.* (2018)

Continued

Table II Continued

Bioactive compound	Model/dosage	Action/mechanism	Reference
Wogonin	Primary endometrial stromal cells from patients with endometriosis Human endometrial stromal cell line (T-HESC)	↓ Cell proliferation ↑ Cell cycle arrest	Ferella *et al.* (2018)
	Balb/c mice (20mg/kg/day by gavage)	↓ Endometriotic lesion size ↓ Cell proliferation ↑ Apoptosis	Ferella *et al.* (2018)
Baicalein	Human endometriotic stromal cells from ovarian endometrioma	↓ Cell proliferation G1 phase cell cycle arrest ↓ Bcl-2	Jin *et al.* (2017)
Parthenolide	Human endometriotic stromal cells from ovarian endometrioma	↓ TNF-α-induced IL-8 release ↓ COX-2 ↓ PGE_2 ↓ Cell proliferation ↓ IκB phosphorylation	Takai *et al.* (2013)
	Balb/c mice (10 mg/kg/thrice weekly)	↓ Number of lesions ↓ Endometriotic lesion size ↓ Cell proliferation ↓VEGF ↓IL-6 ↓MCP-1 ↓ LIF	Takai *et al.* (2013)
Andrographolide	Primary cell cultures of endometriotic stromal cells	↓ Cell cycle progression ↓ Cell proliferation ↓ NF-κB activation ↓COX-2 ↓ Tissue Factor	Zheng *et al.* (2012)
	Sprague–Dawley rats with induced endometriosis (50 or 187.5 mg/kg by gavage)	↓ Endometriotic lesion size ↓ Endometriosis-pain ↓ NF-κB activation ↓ NGF ↓ COX-2	Zheng *et al.* (2012)
Delta-9-tetrahydrocannabinol	C57Bl/6J mice (2 mg/kg/day)	↓ Endometriotic lesion size ↓ Endometriosis-pain ↓ Hyperinnervation	Escudero-Lara *et al.* (2020)

BDNF, brain derived neurotrophic factor; 17β-hsd, 17β-hydroxysteroid dehydrogenase; CA, carnosic acid; E2, oestrogen; EsA, esculentoside A; ESR1, oestrogen receptor 1; HGF, hepatocyte growth factor; IGF-1, insulin-like growth factor-1; IL-1β, interleukin-1β; IL-8, interleukin-8; iNOS, inducible nitric oxide synthase; LIF, leukemia inhibitory factor; MCP-1, monocyte chemoattractant protein-1; NGF, nerve growth factor; P450Arom, aromatase P450; PLGA, poly(lactic-co-glycolic acid); PPD, 20(S)-protopanaxadiol; PPT, 20(S)-protopanaxatriol; PR, progesterone receptor; RA, rosmarinic acid; Rf, ginsenoside Rf; Rg3, ginsenoside Rg3; Rh2, ginsenoside Rh2; T-HESC, human endometrial stromal cell line; TIMP, tissue inhibitor of MMP; TRAIL, tumour necrosis factor-related apoptosis-inducing ligand; TRPV-1, transient receptor potential cation channel subfamily V member 1; VEGF, vascular endothelial growth factor; VEGF-R, vascular endothelial growth factor receptor.

disease and hypertension (Hatamipour *et al.*, 2019). In addition, the oral bioavailability of curcumin may be improved by means of solid dispersions, nanoparticles, polymeric micelles, nanosuspensions and lipid-based nanocarriers (Ma *et al.*, 2019). Moreover, distinct curcumin formulations with excellent human bioavailability and pharmacokinetics data are now available. For instance, NovaSol®, CurcuWin® and LongVida® have been reported to exhibit an over 100-fold higher bioavailability relative to unformulated curcumin (Jamwal, 2018).

Finally, specific plant-derived bioactive compounds have already entered the important stage of clinical evaluation. However, the current study situation is far from sufficient to justify the inclusion of such compounds in modern multimodal treatment concepts for endometriosis. This can only be achieved based on future randomised controlled multi-centre trials including large patient cohorts.

Chinese Herbal Medicine

As one of the major contemporary alternative medicines, traditional Chinese herbal medicine (CHM) is not only of great significance in China, but meanwhile also attracts the academic attention in the world of Western medicine. CHM traditionally uses polypharmacological interactions of herbal formulae with multiple ingredients to treat complex diseases. The idea is that each individual herb works synergistically to treat the disease process (Burks-Wicks *et al.*, 2005). In contrast to

Table III Ingredients of Chinese herbal medicine formulae.

Formula	Ingredients	Reference
PCJNF	Ramulus Cinnamomi, Sanguis Draconis, Faeces Trogopterori, Pollen Typhae, Chinese Eaglewood, *Whitmania pigra* Whitman, *Liriope spicata*, *Glycyrrhiza uralensis* Fisch	Liang *et al.* (2017)
XLF	Fried turtle shells, sliced Cornus Cervi, leech, Eupolyphaga seu Steleophaga, *Vaccaria segetalis*, *Rhizoma curcumae*, steamed buns, *Salvia chinensis*, *Smilax china*, *Radix codonopsis* and *Rhizoma zingiberis* Preparatum	Zhou *et al.* (2019)
WXT	*Typha angustifolia* L., *Trogopterus xanthipes* Milne-Edward, *Draconis sanguis*, Leguminosae, Radix Dipsaci Asperoidis, *Commiphora myrrha*, *Corydalis yanhusuo* W.T.Wang, Fructus Meliae Toosendan	Zhang *et al.* (2013b)
GZFLC GZFLW	Ramulus Cinnamomi, Poria, Semen Persicae, Radix Paeoniae, Rubra or Radix Paeoniae Alba, Cortex Moutan	Zhou *et al.* (2018)
SJZTC	Drac(h)onis sanguis, *Panax pseudoginseng* (saponin), *Thunberg fritillary* bulb (Verticinone), Coix seed	Zou *et al.* (2013)
XCHT	*Bupleurum chinense*, *Scutellaria baicalensis*, ginseng root, Pinellia, licorice, ginger, jujube	Jiao *et al.* (2013)
HYXZ	*Salvia miltiorrhizae* radix, *Morindae officinalis* radix, *Panax notoginseng* radix, *Semen coicis*, *Fritillariae thunberg* bulbus, *Spica prunellae*, *Polygoni aviculare* herba, *Panta rhei* radix, *Alternaria dianthi* herba, *Corydalis* sp. rhizome, *Hirudo* sp., *Typhae* sp. Pollen, *Draconis sanguis*	Chen and Gong (2017)
SZD	Foeniculi Fructus, Zingiberis Rhizoma, Corydalis Rhizoma, Myrrha, Rhizoma Chuanxiong, Angelicae Sinensis Radix, Radix Paeoniae Rubra, Cortex Cinnamomi, Typhae Pollen, Trogopteri Feces	Zhu *et al.* (2018)
JFS	Ligustrazine, ferulic acid and tetrahydropalmatine	Chen *et al.* (2018b)
TSS	*Angelicae radix*, Hoelen, *Cnidii rhizoma*, *Alismatis rhizoma*, Paeoniae Radix, *Atractylodis lancae* rhizome	Nagira *et al.* (2019)
BSHXR	*Astragali radix*, *Angelicae sinensis* radix, Ligustici Chuanxiong Rhizoma, Cuscutae semen, Taxilli Herba, Dipsaci Radix	Ding *et al.* (2018)
DEFK	Salvia, Rhizoma Curcumae, Rhizoma Sparganii, bupleurumroot, angelica, liquorice, Rhizoma Corydalis, Radix Paeoniae Rubra, Rhizoma Cyperi	Li *et al.* (2017)
XFZY	Persicae Semen, Flos Carthami Tinctorii, Radix Angelicae Sinensis, Radix Rehmanniae Glutinosae, Rhizoma Ligustici Chuanxiong, Radix Rubrus Paeoniae Lactiflorae, Achyranthis Bidentatae Radix, Platycodi Radix, Radix Bupleuri, Fructus Aurantii, Radix Glycyrrhizae	Zhang *et al.* (2012)

BSHXR, Bushen Huoxue recipe; DEFK, Danefukang; GZFLC, Gui-Zhi-Fu-Ling Capsule; GZFLW, Gui-Zhi-Fu-Ling-Wan; HYXZ, Hua Yu Xiao Zheng; JFS, Jiawei-Foshou-San; PCJNF, Ping-Chong-Jiang-Ni; SJZTC, Sanjie Zhentong capsule; SZD, Shaofu Zhuyu Decoction; TSS, tokishakuyakusan; WXT, Wenshen Xiaozheng Tang; XCHT, Xiaochaihu Tang; XFZY, Xuefu-Zhuyu capsule; XLF, Xiao Liu Fang.

Western medicine, which focuses on fighting the disease directly, treatment with CHM emphasises the prescription for individual patients' syndrome patterns and holistically attempts to adjust the body's physiology. For example, a part of endometriosis-associated symptoms are summarised in CHM as 'blood-stasis syndrome' (Wieser *et al.*, 2007; Guo *et al.*, 2010), which is reflected by the anti-platelet, anti-thrombotic and anti-coagulation activity of some CHM formulas (Table III). Chinese herbs are generally taken as pills or decoctions (teas) while the design of the formula and the dosage varies. By now, several herbal products are also available for the treatment of endometriosis and infertility.

Formulations for endometriosis treatment

There are several representative classic Chinese herbal prescriptions containing *Cinnamomi ramulus*, an ancient herbal medicine used for thousands of years in China with a broad spectrum of pharmacological activities (Liu *et al.*, 2020). One of them is the formula Ping-Chong-Jiang-Ni (PCJNF, Table III) which is clinically effective on dysmenorreal relief and reduction of CA-125 and prolactin serum levels in endometriosis patients (Liang *et al.*, 2017). *In vitro*, PCJNF suppresses proliferation, migration and invasion while increasing apoptosis in ectopic endometrial stromal cells, which is mediated by JNK signalling (Liang *et al.*, 2017).

A preliminary study reported that the Xiao Liu Fang (XLF, Table III) formula is effective in the treatment of uterine fibroids (Wen, 2007; Liu *et al.*, 2013). *In vitro*, XLF extract has an effect similar to that of gestrinone on ectopic and eutopic endometrial stromal cells of endometriosis patients and endometrial tissue of healthy women, as it inhibits endometrial cell attachment and angiogenesis by reducing the cellular expression levels of ICAM-1, COX-2, MMP-9 and VEGF mRNA (Zhou *et al.*, 2019).

Zhang *et al.* (2016) evaluated the effect of Wenshen Xiaozheng Tang (WXT, Table III) on primary ectopic endometriotic stromal cells. WXT inhibited the proliferation and migration of the cells and induced their apoptotic cell death by the activation of caspases, by reducing NF-κB activation, thus lowering the expression of NF-κB-regulated gene products such as cellular inhibitor of apoptosis protein (c-IAP)1, c-IAP2, X-linked inhibitor of apoptosis protein, survivin, myeloid leukemia cell differentiation protein (Mcl)-1, COX-2 and MMP-9 (Zhang *et al.*, 2016). *In vivo*, WXT significantly decreased the mean size of endometriotic lesions as well as the peritoneal fluid and serum levels of TNF-α and IL-1β in a rat model of endometriosis. In addition, it down-regulated the expression of COX-2, MMP-9, plasminogen activator inhibitor and ICAM-1 and up-regulated the expression of TIMP1 within the lesions, indicating that WXT inhibits the production of pro-inflammatory cytokines and regulates the expression of invasion-related genes in endometriosis (Zhang *et al.*, 2013b).

Gui-Zhi-Fu-Ling-Wan (GZFLW, Table III) is one of the most frequently prescribed CHM that has been used in the therapy of women with endometriosis to relieve inflammation-related symptoms (Fang et al., 2012). Gui-Zhi-Fu-Ling capsules (GZFLC) originate from the classic Chinese medicinal formula GZFLW, which is more convenient to be taken and easily accepted by the majority of patients (Zhou et al., 2018). A few studies have been conducted to investigate the effects of GZFLC in relation to the metabolic changes in pelvic endometriosis. Ji et al. (2011) evaluated autologous endometrial explants in a rat model of surgically induced endometriosis and observed that the volume of developing endometriotic lesions was significantly reduced in the GZFLC treatment group when compared to controls. This was associated with ICAM-1 and MCP-1 down-regulation within the lesions. Moreover, the numbers of $CD4^+$ T lymphocytes and the activity of natural killer cells were higher than in the control group (Ji et al., 2011). In the same model, TUNEL assays showed that different doses of GZFLC induce apoptosis in endometriotic cells. GZFLC further inhibited the mRNA levels of the anti-apoptotic Bcl-2 gene and increased the mRNA levels of the pro-apoptotic factor Bcl-2-associated X protein. These results indicate that GZFLC inhibits cell proliferation and induces apoptosis of endometriotic cells through the mitochondrial apoptotic pathway (Hu et al., 2014). Furthermore, proton nuclear magnetic resonance spectroscopy-based targeted metabolite profiling demonstrated that GZFLC significantly affects the expression levels of transforming growth factor (TGF)-β1, glucose transporter (GLUT)-4 and VEGF, indicating that GZFLC also affects endometriosis by influencing glycolysis and gluconeogenesis (Zhou et al., 2018).

Sanjie Zhentong capsule (SJZTC, Table III) exhibits immunoregulatory and anti-inflammatory activity and relieves pain. In a rat model of surgically induced endometriosis, SJZTC reduced the size of endometrial explants, most likely by inhibiting the expression of VEGF and TNF-α (Zou et al., 2013).

Another classic Chinese herbal formulation with anti-inflammatory and immunoregulatory effects is Xiaochaihu Tang (XCHT, Table III) (Jiao et al., 2013; Zhao et al., 2017). XCHT exerts a therapeutic effect on endometriosis in rats through the reduction of MMP-2 and MMP-9 activity in ectopic endometrial tissue (Jiao et al., 2013).

In clinical practice, it has been observed that Hua Yu Xiao Zheng (HYXZ, Table III) decoction alleviates endometriosis-associated symptoms, including severe dysmenorrhea, dyspareunia, menstrual irregularities and infertility (Chen and Gong, 2017). *In vivo*, this formula decreases the size of endometriotic lesions in rats and affects angiogenesis through reduction of VEGF and angiopoietin-2 expression (Chen and Gong, 2017).

In Taiwan, one of the top five commonly used herbal formulas for the treatment of endometriosis is the Shaofu Zhuyu Decoction (SZD, Table III), a classic traditional Chinese medicine for dysmenorrhea, which has also been widely used in clinical practice to relieve symptoms of endometriosis (Tsai et al., 2017). In a rat endometriosis model, SZD significantly reduced the size of ectopic lesions, inhibited cell proliferation, increased apoptosis and reduced microvessel density and hypoxia-inducible factor expression within the lesions (Zhu et al., 2018).

Jiawei-Foshou-San (JFS, Table III) formula has been demonstrated to diminish the growth of endometriotic lesions, reduce oestrogen levels and suppress inflammation and angiogenesis in rats (Tang et al., 2014). Chen et al. (2018b) developed an autologous transplantation model for the induction of endometriosis in rats to evaluate the *in vivo* effect of JFS. They observed that JFS significantly suppresses the growth and reduces the volume of ectopic endometrium. Moreover, JFS inhibited the gene expression of MMP-2, MMP-9 and up-regulated the mRNA levels of TIMP-1 (Chen et al., 2018b).

CHM has already been used to treat patients with endometriosis with favourable effects on disease-related symptoms and fertility (Ried and Stuart, 2011; Bina et al., 2019). In fact, a Cochrane study evaluating randomised controlled trials reported that post-surgical administration of CHM may be comparably effective as gestrinone but with fewer side effects (Flower et al., 2012). Moreover, treatment with CHM may be even better than danazol (Flower et al., 2012). In addition, it was suggested that CHM results in higher pregnancy rates when compared to Western medical fertility drug therapy (Ried, 2015).

In a randomised multi-centre trial involving 208 patients, CHM was compared with Western medicine for the treatment of endometriosis (Zhao et al., 2013). The CHM-treated groups received three types of formulations based on their particular syndrome differentiation. Patients in the Western medicine group were treated with GnRHa or gestrinone. Treatment was started by administration of the drugs to the patients during days 1–5 of their first menstruation in both groups. The patients with stages I and II of endometriosis were treated for 3 months, while the patients with stages III and IV were treated for 6 months (ASRM, 1997). Although, the incidence and timing of recurrence of the disease were not significantly different between the two groups, the first pregnancy in the CHM group was significantly earlier than the first pregnancy in the Western medicine group. Moreover, CHM had some advantages, such as low incidence and mild symptoms of adverse reactions as well as good patient compliance (Zhao et al., 2013).

In a large study carried out in Taiwan, the utilisation of CHM among women with endometriosis was analysed. For this purpose, a randomly sampled cohort of 1 000 000 beneficiaries recruited from the Taiwan National Health Insurance Research Database was evaluated and 14 080 study subjects were included in the study. Among them, 12 788 (90.8%) endometriosis patients used CHM at least once during the 11-year study period. Patients suffering from the symptoms of endometriosis were more likely to choose CHM treatment than those with no symptoms. GZFLW was the most frequently prescribed CHM among users. The potential effects of these Chinese herbs when used to treat endometriosis are related to their anti-inflammatory, anti-proliferative and pain-alleviating properties (Fang et al., 2012). Despite the very large number of subjects involved in this study, the non-randomised and uncontrolled methodology of the studies prevents definitive conclusions and emphasises the need for well-conducted, double-blind, randomised, placebo-controlled studies to further evaluate the efficacy of GZFLW and other medicinal herb formulations on women with endometriosis (Guo et al., 2010). Due to the limitations of this work, the authors suggested that the results could have been confounded by a placebo effect (Fang et al., 2012).

More recently, Tsai et al. (2017) conducted an additional study with the objective to identify a CHM network for endometriosis by analysing the same nationwide CHM prescription database in Taiwan. From 2008 to 2013, a total of 33 235 endometriosis patients were identified and 31 650 patients used CHM at least once for any reason. Among all herbal formulae, GZFLW was used most frequently (28.1% of all

prescriptions) and *Cyperus rotundus* was the most commonly used single herb (18.8% of all prescriptions) (Tsai *et al.*, 2017).

An additional Taiwanese population-based retrospective cohort study evaluated the relationship between the use of CHM and subsequent surgery among patients with endometriosis (Su *et al.*, 2014). A total of 8283 CHM users were identified among the 22 488 endometriosis patients found in the National Health Insurance reimbursement database between 2000 and 2010, while a control group consisted of 8283 women with endometriosis who were non-users of CHM. The treated group included subjects, who had received an orally administered CHM treatment for more than 2 consecutive weeks. This study found that in endometriosis patients, the incidence rate and risk of surgery were both lower among CHM users than among non-users. Moreover, surgery was performed earlier in the group of non-users than in the group of CHM users. Hence, CHM appears to provide an alternative treatment option that reduces the incidence of surgery and, thus, could have important health economic implications (Su *et al.*, 2014).

Another clinical study performed by Ding and Lian (2015) evaluated a total of 80 patients treated with hormone or traditional CHM. Patients belonging to the hormone therapy group took 12.5 mg mifepristone orally every day. The therapy started from the 1st day of their menstrual cycle and lasted for 6 months. In the traditional Chinese medicine group, two kinds of herbal mixtures were given to the patients in different periods of their menstrual cycle. The first one was applied before ovulation, while the other was given after ovulation. After water decoction, each herb was taken separately in the morning and evening (Ding and Lian, 2015). After treatment, serum oestradiol, FSH and CA-125 levels decreased. In addition, CHM has demonstrated to be safe. No significant changes on serum levels of glutamic-pyruvic transaminase and creatinine were found. At the same time, there were no severe adverse events during the follow-up treatment and the pregnancy rate was similar in both groups. There were no cases of ectopic pregnancy and no significant differences in spontaneous abortion rate were observed. Despite the limitations of this approach (small sample size and the fact that surgery was not taken into account), the study provided preliminary data that this two-staged herb therapy is a safe and effective measure for endometriosis patients with infertility (Ding and Lian, 2015).

Bushen Huoxue recipe (BSHXR, Table III) is a classic Chinese herbal prescription for nourishing the kidney and activating blood circulation, traditionally used to treat failed pregnancy and its complications (Ding *et al.*, 2018). In a meta-analysis including a total of 936 patients, it was observed that BSHXR does not significantly differ from Western medicine in terms of improving endometriosis-associated pain. However, BSHXR significantly enhanced the clinical pregnancy rate. In addition, although six trials described serious events, less adverse effects of BSHXR were reported when compared to Western medicine (Shan *et al.*, 2017).

Danefukang (DEFK, Table III) is a manufactured decoction based on CHM formula, and is currently an over-the-counter drug with indications for dysmenorrheal, menstrual disturbances (Guo *et al.*, 2010). DEFK soft extract is the first CHM formula that received a national (Chinese) drug approval number for the treatment of endometriosis (Li *et al.*, 2017). A meta-analysis of 39 randomised controlled trials enrolling 5442 patients was carried out to evaluate the efficacy and safety of DEFK soft extract in the treatment of endometriosis (Li *et al.*, 2017). The results revealed that DEFK soft extract was more efficient than gestrinone in the treatment of endometriosis and its efficacy was comparable to that of danazol and mifepristone. In terms of the relapse rate and relieving dysmenorrhea, DEFK soft extract was also as effective as gestrinone and mifepristone, and the incidence of adverse reactions was lower than that of conventional Western medicines. In conclusion, DEFK soft extract offers certain advantages in endometriosis treatment. However, because the methodological quality of the studies included in this analysis was low, rigorously designed and strictly implemented randomised controlled trials are required to further validate the efficacy of DEFK (Li *et al.*, 2017). For instance, a recent report of Zhong *et al.* (2019) analysed the efficacy of DEFK soft extract for the treatment of symptoms associated with endometriosis. A total of 174 patients with endometriosis were randomly divided into a group treated with DEFK or a control group treated with mifepristone. Both groups were treated for 3 months. The effectiveness rate was significantly superior in the DEFK group than in the mifepristone control group and treatment with DEFK resulted in a greater improvement in quality of life (improved symptoms, attenuated depression and anxiety). Moreover, DEFK treatment resulted in a decrease in the levels of the pro-inflammatory cytokines TNF-α and IL-6 and reduced CA-125 levels compared with mifepristone. In conclusion, it was suggested that DEFK is a meaningful option for patients with endometriosis (Zhong *et al.*, 2019).

Currently, the ClinicalTrials.gov website lists endometriosis as one of the diseases included in a large recruiting randomised interventional clinical trial (720 participants) comparing the CHM Xuefu-Zhuyu capsule (XFZY, Table III) administered at 2.4 g (6 capsules) three times daily for 12 weeks with placebo (Wang, 2020b). The primary outcome are changes in the Chinese Medicine patient-reported-outcome scale in patients with Qi Stagnation and Blood Stasis Syndrome, characterised by symptoms such as different types of pain, irritability or depression, insomnia and chest tightness, among others (Hu *et al.*, 2015). Pain, self-rating anxiety scale, self-rating depression scale and Quality of Life Scale are listed as secondary outcomes along with an ambitious monitoring of gene expression and biochemical parameters. Notably, XFZY has been used in CHM as a treatment of primary dysmenorrhea, indicating a possible link to endometriosis (Leem *et al.*, 2019).

Nowadays, ancient formulations of CHM and Kampo (Japanese) medicines coexist and complement each other. The herbs used in Kampo are commonly used for making decoctions and herbal preparations from a single crude ingredient or a mixture of multiple crude ingredients (Teng *et al.*, 2016). Among them, tokishakuyakusan (TSS, Table III) is a representative Kampo mixture, which is widely prescribed in Japan for patients with gynecological disorders (Nagira *et al.*, 2019). TSS has been shown to reduce the severity of primary and secondary dysmenorrhea (Oya *et al.*, 2008; Yoshino *et al.*, 2016) and to alleviate menstruation-related headaches that are refractory to conventional treatments (Akaishi *et al.*, 2019). In Balb/c mice with induced endometriosis, TSS treatment significantly reduced lesion number and size, and improved sensitivity to nocifensive stimuli. It was assumed that paeoniflorin contained in paeoniae radix is the main component responsible for the antinociceptive of TSS (Nagira *et al.*, 2019). In a recent *in vitro* study, Takeuchi *et al.* (2020) further observed that TSS has anti-inflammatory and anti-angiogenic effects on endometriosis by controlling IL-8 and VEGF secretion in endometriotic stromal cells.

Table IV CHM formulae evaluated in experimental models of endometriosis.

Formula	Model/dosage	Action/mechanism	Reference
Ping-Chong-Jiang-Ni (PCJNF)	Human ectopic endometrial stromal cells	↓ Cell proliferation ↓ Invasion ↓ Cell migration ↑ Apoptosis	Liang *et al.* (2017)
Liu Fang (XLF)	Human ectopic and eutopic endometrial stromal cells from patients with endometriosis	↓ Attachment ↓ Angiogenesis ↓ ICAM-1 ↓ COX-2 ↓ MMP-9 ↓ VEGF	Zhou *et al.* (2019)
Wenshen Xiaozheng Tang (WXT)	Human ectopic endometrial stromal cells	↓ Cell proliferation ↑ Apoptosis ↓ NF-κB ↓ Cell migration	Zhang *et al.* (2016)
	Sprague-Dawley rats	↓ Endometriotic lesion size ↓ IL-1β ↓ TNF-α ↓ ICAM-1 ↓ COX-2 ↓ MMP-9 ↑ TIMP-1	Zhang *et al.* (2013b)
Gui-Zhi-Fu-Ling Capsule (GZFLC)	Sprague-Dawley rats	↓ Endometriotic lesion size ↓ ICAM-1 ↓ MCP-1 ↓ $CD4^+$ lymphocytes ↓ Natural killer cell activity	Ji *et al.* (2011)
	Sprague-Dawley rats	↑ Apoptosis ↑ Bax ↓ Bcl-2 ↓ Cell proliferation	Hu *et al.* (2014)
	Wistar rats	↓ GLUT-4 ↓ VEGF ↓ TGF-β	Zhou *et al.* (2018)
Sanjie Zhentong capsule (SJZTC)	Lewis rats	↓ Endometriotic lesion size ↓ VEGF ↓ TNF-α	Zou *et al.* (2013)
Xiaochaihu Tang (XCHT)	Sprague-Dawley rats	↓ MMP-2 ↓ MMP-9	Jiao *et al.* (2013)
Hua Yu Xiao Zheng (HYXZ)	Sprague-Dawley rats	↓ Endometriotic lesion size ↓ Angiogenesis ↓ VEGF ↓ Angiopoietin-2	Chen and Gong (2017)
Shaofu Zhuyu Decoction (SZD)	Sprague-Dawley rats	↓ Endometriotic lesion size ↓ Cell proliferation ↑ Apoptosis ↓ Angiogenesis ↓ HIF-1α	Zhu *et al.* (2018)
Jiawei-Foshou-San (JFS)	Sprague-Dawley rats	↓ Endometriotic lesion size ↓ Invasion and metastasis Regulation of epithelial-mesenchymal transformation	Chen *et al.* (2018b)
Tokishakuyakusan (TSS)	Balb/c mice	↓ Endometriotic lesion number ↓ Endometriotic lesion size ↓ Endometriosis-pain	Nagira *et al.* (2019)
	Human ectopic endometrial stromal cells	↓ IL-8 ↓ VEGF	Takeuchi *et al.* (2020)

Bax, Bcl-2-associated X protein; Bcl-2, B cell lymphoma-2; Glut-4, glucose transporter type 4; HIF-1α, hypoxia-inducible factor-1; TGF-β, transforming growth factor β.

Summary

As summarised in Table IV, different CHM formulations have been shown to target multiple cellular processes that are crucially involved in the pathogenesis of endometriosis, such as inflammation, oxidative stress and apoptosis. Hence, they have also been demonstrated to effectively inhibit the development and growth of endometriotic lesions in different animal models of the disease. Additional clinical findings indicate that CHM may be particularly beneficial to treat endometriosis-associated symptoms, such as pain. In this context, all published studies reported that CHM has at least the same efficacy as the standard Western medicine with fewer side effects. However, the underlying mechanisms remain elusive so far. Moreover, it should be noted that in the past most clinical trials on the use of traditional Chinese medicine to treat endometriosis have been judged to be of poor quality due to substantial flaws in evaluating outcome measures, follow-up, diagnosis, data analysis, reporting of adverse effects and randomisation (Guo *et al.*, 2010). Indeed, in over 850 CHM studies of endometriosis analysed by Guo *et al.* (2010), only 18.0% achieved evidence Level II, and none had a Jadad score >3, which is considered the minimum standard for inclusion in a systematic review or meta-analysis. Hence, additional convincing evidence is needed to prove the suitability of CHM for endometriosis treatment. If this succeeds, the integration of CHM into Western medicine could be a promising approach in the future multi-modal management of endometriosis.

Conclusions

The herein described preclinical and clinical studies indicate that natural plant-derived agents represent promising candidates for the development of novel treatment strategies in the management of endometriosis. They typically exhibit a pleiotropic action profile, which simultaneously targets fundamental processes in the complex pathophysiology of the disease, such as proliferation, apoptosis, inflammation, ROS formation and angiogenesis. Hence, they may help to prevent escape mechanisms, as they are frequently observed in response to targeted therapy. Moreover, they may induce less severe side effects when compared to conventional anti-oestrogenic compounds. In addition, they bear the chance to introduce affordable therapeutics into the market, which is a big issue in all countries given the continuously rising worldwide healthcare costs.

However, there are still many hurdles to overcome for the successful implementation of natural treatment strategies in daily clinical practice. The heterogenous and often combinatorial nature of the natural compounds makes it difficult to differentiate cause from effect in the readouts of numerous experimental studies, and the exact mechanism of action is often unknown. Moreover, pharmacokinetics and pharmacodynamics have not been carefully addressed in many of the preclinical studies, and herb–drug interactions need to be carefully studied when the natural compounds are combined with conventional pharmacotherapy. Indeed, their efficiency and safety has to be proven in comparison to conventional therapeutic approaches in randomised controlled multi-centre trials. However, for this purpose it is necessary to establish standardised protocols for the GMP-compliant generation of well-defined plant extracts. In this context, it should also be considered that many herbs or herbal compounds may not be patentable or their patents may have expired a long time ago. Hence, there is no incentive for pharmaceutical industry to drive the development in this field or even to conduct expensive clinical trials. Another important issue is the fact that most phytochemicals exhibit a poor stability and bioavailability in their natural form and, thus, may primarily serve as lead compounds for the development of novel drugs with improved pharmacokinetic profiles (Phan *et al.*, 2018). Finally, it should be noted that natural-based therapies, particularly CHM, primarily focus on the improvement of endometriosis-related symptoms but not on the cure of the disease. This may also be a major reason why even within China itself CHM is not accepted and approved by all gynaecologists and patients (Guo *et al.*, 2010). Moreover, it is unlikely that natural-based therapies will ever serve as a stand-alone therapy. However, they bear great potential as an integral part of future multi-modal treatment concepts for endometriosis. This is underscored by the rapidly growing interest and demand for these therapies by not only endometriosis patients but also their attending physicians.

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Authors' roles

G.F.M. formulated the primary draft of the manuscript and primarily carried out the PubMed searches, analysed the data and drafted the tables, M.G. supervised the conception, design and development of all aspects of the article, carried out the Clinicaltrials.gov searches, designed the figures and was involved in the data analysis and interpretation. M.W.L. made substantial contributions to design, analysis and interpretation of data. Development of the article, review, editing and final approval of the final article was by G.F.M., M.G. and M.W.L.

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Conflict of interest

All authors declare that no conflict of interest exists.

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