Medicinal & Aromatic Plants
ISSN: 2167-0412

Harris and Vlass, Med Aromat Plants 2015, 4:2
DOI: 10.4172/2167-0412.1000184

Research Article Open Access

Can Herbal Medicines Improve Cellular Immunity Patterns in Endometriosis?

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Abstract

Endometriosis is a heterogenous, and oestrogen dependant inflammatory disease that is characterised by morphological and biologically active endometrium (composed of endometrial-type glandular tissue and stroma), that is present in sites outside of the uterine cavity. The disease is complex in nature with the implantation of tissue occurring due to phenomena known as retrograde menstruation. While this is considered central to the pathogenesis of endometriosis, 90% of women that experience this event do not have endometriosis, while the remaining 10% of this population do have endometriosis. The role of the immune system may explain why some women develop endometriosis and why others don't. Alterations in the immune system (Increased TNF-α, PGE2 and reduced NK cells) have been proposed to play a key role in the establishment of endometrial implants and sustained its growth and development.

In order to treat aspects of immunity, it is important to improve relative oestrogen excess which triggers a pro-inflammatory cascade and to regulate immune system abnormalities. With continued unopposed oestrogens, the immune system will not regulate, so this must be a primary treatment aim. Prostaglandin synthesis must be regulated to ensure normal uterine function, healthy flow of menstruation and reducing pain experienced. Key herbs that help address inflammation, immune alterations and oestrogen clearance include Turmeric, Echinacea, Green tea, Caledula and Gotu cola. These herbs have multi-factorial actions that address the underpinning pathology of endometriosis and help rectify and improve reproductive function.

Keywords: Endometriosis; Immunology; Oestrogen; Macrophages; Herbal Medicine

Endometriosis Pathophysiology

Endometriosis is a heterogeneous, and oestrogen dependant inflammatory disease that is characterised by morphological and biologically active endometrium (composed of endometrial-type glandular tissue and stroma), that is present in sites outside of the uterine cavity [1]. The condition almost exclusively occurs in women in the reproductive years [2]. The most common locations for endometriotic deposits are the ovaries and pelvic peritoneum. Sites by which this type of tissue attaches include the uterosacral ligaments 63%, ovaries superficial 56% and deep 20%, ovarian fossa 33%, anterior vesicle pouch 22%, Pouch of Douglas 19% and Intestines 9% [3]. The location and inflammatory response to these lesions are believed to play a key role in the manifestation of the signs and symptoms of endometriosis. The common histological features of endometriosis are endometrial stromal or epithelial cells, chronic bleeding and signs of inflammation. It is important to note that endometriosis shares a number of features that are common to that of neoplasms including uncontrolled growth, angiogenesis, and invasion of adjacent tissues, defective apoptosis and sustained local inflammatory responses [4].

The disease is complex in nature with the implantation of tissue occurring in the first instance due to phenomena known as retrograde menstruation first described by Sampson in 1927 [5]. While this is considered central to the pathogenesis of endometriosis, 90% of women that experience this event do not have endometriosis, while the remaining 10% of this population do have endometriosis [6,7]. The role of the immune system may explain why some women develop endometriosis and why others don't. Alterations in immune function have been proposed to play a critical role in the establishment of endometrial implants and its sustained growth and development [7]. The mechanisms by which endometrial cells bind to extragenital sites are due to alterations in cell adhesion molecules (CAMs). The most noted CAMs involved in endometriosis are the integrins and the cadherins, which initiate adhesion. CAMs have been under significant focus recently in terms of determining the underpinning pathogenesis of endometriosis. It has been shown that alterations in the endometrial and peritoneal CAMs facilitate the binding of retrograde menstruated endometrium [8]. Integrins have been shown to form cell surfaces with membrane metalloproteinases-2 and -9 (MMPs) to facilitate matrix degranulation and motility, thereby facilitating cellular invasion allowing a process for the retrograde menstrual endometrium to gain access to extragenital sites [9].

To date there has been limited information provided on the benefits of herbal medicine in the treatment of endometriosis. The aim of the current review is to; Review the current state of knowledge for the pathogenesis of endometriosis and the role of the immune system in the causation of the disease and to provide a rationale for the use of a range of different herbal medicines that may be beneficial in the treatment of endometriosis.

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Received January 24, 2015; **Accepted** March 04, 2015; **Published** March 08, 2015

Citation: Harris T, Vlass AM (2015) Can Herbal Medicines Improve Cellular Immunity Patterns in Endometriosis? Med Aromat Plants 4: 184. doi:10.4172/2167-0412.1000184

Oestrogen, Inflammation and Endometriosis

Oestrogen plays a critical role in endometriosis. Although endometriosis is a multifactorial disease a large amount of research points towards oestrogen being involved in the establishment and maintenance of this disease [4,10,11]. Oestrogen promotes a feedback mechanism, which induces key steroidogenic genes most notably aromatase (catalyses the conversion of testosterone to oestrogen) and the over expression of cyclo-oxygenase 2 (produces the prostaglandin E2) that promotes local inflammation. Inflammation has doubled edged sword, as it triggers the regulated destruction of tissues, but it also initiates and guides endometrial repair [4]. Oestrogens in particular have recently been shown to act on signalling pathways of macrophages that sustain the underlying inflammation, causing the release of a range of cytokines (most notably TNF-α) that perpetuate the inflammatory response [4].

There are a number of sites in the body that produce oestrogen supporting the inflammation in endometriosis, including; Oestradiol (E2) secreted by the ovary reaches endometriotic tissue through the circulation, Follicular rupture during ovulation causes spillage of large amounts of E2 directly onto endometrial implants that are in the pelvis, Aromatase in adipose tissue catalyses the conversion of circulating androstenedione to oestrone (E1) that is subsequently converted to E2 form – which can enter the circulation and reach endometrial tissue.

There is building evidence in the literature that supports a role for the immune system in the pathophysiology of this condition [7,9,12]. The capability of these cells to implant on extra-genital sites is most likely due to hormonal and immunological factors that lead to failure of the immune system to eliminate cells from inappropriate binding sites [13]. Alterations in cellular immunity together with inflammation allows for the retrograde endometrial cells to invade and survive in foreign sites outside of the reproductive system.

Cellular Immunity and Inflammation

As indicated above inflammation is a key component to the pathogenesis of endometriosis similar to many other chronic diseases (arthritis and cardiovascular disease), where perpetuation of inflammation drives its pathology [7,12]. Alterations in inflammatory mediators promote the formation of fibrotic adhesion allowing for the growth and spread of more endometrial tissue [14]. These mediators (particularly COX-2 and TNF-α) also promote steps involved in angigogenesis, which supplies the abnormal tissue with a blood and nutritional supply. Off these mediators over production and under production of certain cytokines, prostaglandins, peritoneal macrophages (increased), T cell (decreased) and natural killer (NK) cells (decreased). Each of these immunological components has been explained below:

Natural killer cells: The mechanism by which retrograde endometrial cells are cleared from the peritoneal cavity is poorly understood. It is likely that the reduced activity of NK cells plays a central role [15] given the biological role they have in immune surveillance. In general NK cells play an important role in human reproduction and disturbance in their function can lead to the development of gynaecological disorders (their function has been reviewed extensively by Sikora) [16]. In endometriosis there is decreased cytotoxicity of peripheral and peritoneal NK cells together with reduced activity of these cells [16]. This indicates that the first lines of defence is compromised and unable to communicate with the rest of the immune system and unable to detect and assist the clearance of the retrograde endometrial cells. Thus, creating an environment for the retrograde endometrial cells to become established within the peritoneal cavity.

The question remains if the number and activity of these cells could be adjusted could the progression of the disease be halted?

Activation of peritoneal macrophages: Monocytes of macrophages have been implicated in endometriosis since there number and activity are increased and are now considered central to the development of endometriosis [4,15]. These cells appear to impair cellular immunity [15,17] by releasing growth factors and cytokines that allow for greater survival and growth of ectopic endometrial cells.

Macrophages are an important first line of defence against infections and foreign bodies. When activated macrophages secrete a number of pro-inflammatory cytokines including TNF-α, IL-1, IL-12 and IL-6 (the role of each cytokine relevant to endometriosis is described in Table 1). These macrophages are referred to as classically activated/inflammatory macrophage (or M1 cells). Uncontrolled classical activation results in defective healing and persistent inflammation [4]. The persistent inflammation accounts for the high levels of cytokines such as TNF-α reported in the peritoneal fluid of women with endometriosis [4].

Macrophages also have the capacity to undergo an alternative activation pathway (secreting products including MMPs, IGF-1, PTX3, TGF-β and PGE2) that tune inflammatory responses, scavenge debris and promote angiogenesis, tissue remodelling and repair; and are referred to as alternatively activated or M2 cells [4]. Peritoneal macrophages are a well-characterized source of vascular endothelial growth factor (VEGF) and ovarian steroids that regulate the production of growth factor [18]. Angiogenesis is a pre-requisite for endometrial lesions to establish and grow. This process is dependent

Cytokines	Immunology Characteristic in Endometriosis
TNF-α	TNF-α is a major product of macrophages and promotes continuous inflammation in the fallopian tubes leading to inflammatory proteolysis of the extracellular matrix. This results in tissue repair, fibrosis and scarring of the fallopian tubes – which impairs function of the reproductive tract, leading to poor quality of oocytes. TNF-α also promotes the secretion of other pro-inflammatory cytokines including IL-1, IL-6 and additional TNF-α. TNF-α also induces Matrix metalloproteinase (MMPs), with its expression being paralleled to the development of ectopic lesions.
IL-1	Increased concentrations of IL 1 attract monocytes and macrophages into the peritoneal fluid that bathes the reproductive organs. IL-1 promotes angiogenesis in endometrial lesions, thus allowing a blood flow and nutrition source for this foreign tissue. IL-1 also interferes with peritoneal immune surveillance.
IL-6	IL-6 from peritoneal fluid have been well correlated with the severity of endometriosis. The receptor for IL-6 is reduced in endometriosis, which is believed to contribute to the resistance of endometrial implants to growth inhibition caused by IL-6. So in this sense high levels of IL-6 are trying to reduce the growth of implants but due to the loss of receptors the IL-6 are unable to co-ordinate its biological action.
IL-8	IL-8 is increased in the peritoneal fluid of women with endometriosis. IL-8 acts as an autocrine growth factor and promotes cell attachment, cell growth and stimulates more secretion of it.
Transforming growth factor	This growth factor induces angiogenesis, inhibits T and B lymphocytes and NK cell activity. Thus, impairing the immune system and preventing it from removing the foreign endometrial growth.

Table 1: Role of cytokines in the pathophysiology of endometriosis.

on the activation of macrophages, since experimental models have shown that depletion of macrophages jeopardizes VEGF generation and disturbs neovascularization [19]. A long line of evidence indicates that macrophages are responsible for the angiogenic switch, which increases density of vessels and initiates establishment of vasculature and subsequent remodelling of the vessels [20].

Oestrogens act on a number of these signalling pathways in macrophages, which influence the recruitment of inflammatory cells through the release of TNF- α and the remodelling of inflamed tissues. This remodelling occurs due to mitogen-activated protein kinase (MAPK), phosphatidylinositide-3-kinase/protein kinase B (PI3K/AKT), and nuclear factor-kappa B (NF-κB): as a consequence, a deregulated response to steroids might influence the survival of ectopic endometrial cells and promote the vascularization of the lesions [21,22].

Increased levels of prostaglandins: Prostaglandins play an in important role in the pathology of endometriosis. PGE2 concentration is increased in women with endometriosis, causing the pelvic pain and increased availability of oestrogens and promotes angiogenesis [4]. COX-2 activity is increased in endometriosis, contributing to the production of PGE2. PGE2 is a potent stimulator of aromatase, which has been found in high concentrations in ectopic cells and catalyses the conversion of testosterone to oestradiol, which drives greater activity of COX-2 and inflammation in endometriosis. Research shows that there is a correlation with the severity of endometriosis and the concentration of PGE2 and VEGF [23]. PGE2 promotes angiogenesis by increasing the expression of VEGF, thus allowing the tissue to establish a blood flow and nutritional supply.

Altered cytokine production: The cytokine profile has been well researched in women with endometriosis [23]. The peritoneal fluid of women with endometriosis compared to women without the disease has shown increased concentration of pro-inflammatory cytokines, including: IL-1, IL-4, IL-6, IL-8, IL-10, Reactive oxygen species, Soluble intracellular adhesion molecules, Transformational growth factor, TNF-α.

The following cytokines have been shown to be decreased in women with endometriosis: IL-2, IL-5, IL-13, INF-gamma.

The cytokine profiles from a global point of view results in failure of the immune system to remove ectopic endometrial cells [6,24-26]. Increased concentration of these cytokines (particularly IL-1, IL-4, IL-6, IL-10 and tumor necrosis factor) have been observed in patients with endometriosis and are secreted by both macrophages and endometrial cells [27-34]. It is now believed that the altered cytokine profiles also have adverse effects on the oocyte, spermatozoa, embryo and fallopian tubes thus explaining the links between endometriosis and infertility [23]. Table 1 below explores the most important cytokines and their links to endometriosis.

Herbal Medicines for the Treatment of Endometriosis Associated Cellular Immunity Patterns

Turmeric (*Curcuma longa*)

Actions Include: Anti-inflammatory, Antioxidant Pathways, Hormone modulating, Anti-oestrogenic, Anti-angiogenesis, Anti-proliferative, Cholagogue.

Numerous research studies have found that curcumin inhibits the enzymes cyclooxygenase-2 and lipoxygenase enzymes. Curcumin reduces a range of inflammatory cytokines released from activated macrophages and ectopic endometrium, including TNF-alpha, IFN-gamma, IL 1 and 6 by supressing NF-kappaB activation [32,35,36].

Turmeric has been shown to benefit a range of conditions that involve perpetuation of inflammatory pathways (including cardiovascular disease, diabetes and endometriosis). Blocking TNF- α prevents local inflammation and macrophage recruitment. In addition this results in a reduction in the cell surface and protein expression of intercellular adhesion molecule-1 and vascular cell adhesion molecules, which contributes to an arrest of the growth of ectopic endometrium [37]. The anti-angiogenesis and anti-proliferative actions are important since they reduce the blood flow and further growth and development of endometrial tissue. Studies in rats have shown that curcumin also reduces the production of enzymes (MMP-2, MMP-3 and MMP-9 activity) that cause the breakdown of extracellular matrix and increase tissue inhibitor of metalloproteinase, which arrest the potential of retrograde endometrial cells taking up residences outside the uterine cavity and prevent the further growth of ectopic endometrial cells [32,35,36].

Curcumin also reduces estradiol production in the ectopic endometrium and thus impedes the growth and development of the tissue [38-40]. In addition to the local actions of turmeric at this level it also acts in the liver to assist both phase I and II liver detoxification and thus regulate the clearance of oestrogen. This is an important consideration to treatment as reducing the systemic levels of oestrogen, which potentiate further growth and development of the ectopic endometrium [41].

Curcumin is safe, non-toxic, and mediates its anti-inflammatory effects through the down-regulation of inflammatory transcription factors, cytokines, redox status, protein kinases, and enzymes that all promote inflammation [42].

Green tea (*Camellia sinensis*)

Actions Include: Antioxidant, Anti-angiogenesis, Anti-inflammatory, Anti-adhesive.

To date there are no human studies that have determined the effects of green tea on women with endometriosis. Various *in vitro* and *in vivo* studies have shown that ECGC can be beneficial in the management of endometriosis, as it can inhibit the development, growth and spread of the condition [43-47]. Epigallocatechin-3-gallate (EGCG) has an anti-angiogenesis mechanism and suppressed VEGFC/VEGFR2 expression and signalling pathway in an endometriosis model *in vivo* [45]. ECGG not only has a strong anti-angiogenetic effect, but also inhibits adhesion of endometriotic lesions and reduces the size of the endomtriotic lesions [43-47]. Laschke MW, et al., showed that EGCG has a range of beneficial effects in endometriosis, including: Inhibition of E2-stimulated activation, proliferation and VEGF expression of endometrial cells, Reduces angiogenesis and blood perfusion of ectopic endometrial tissue, Induces the regression of endometriotic lesions.

Calendula (*Calendula officinalis*)

Actions Include: Astringent, Antimicrobial, Lymphatic cleanser, Anti spasmodic, Anti inflammatory/Anti congestive, Immune modulator, Astringent, Anti-microbial, Mildly oestrogenic (modulating) [46] Vulnerary.

Triterpenoid secondary metabolites provide both anti-inflammatory effects and to improve the immune response. Its effects may be mediated by the inhibition of pro-inflammatory cytokines and

COX-2 and subsequent prostaglandin synthesis [48]. Polysaccharide fraction in calendula flowers show moderate immune-stimulating activity [49] and enhance phagocytosis of human granulocytes [50]. The antimicrobial properties may aid any associated endometriosis genitor-urinary infections and this may assist with reducing general immune activation and response [51].

Calendula has been traditional used to assist lymphatic drainage, waste removal and improve wound healing [52,53]. This is thus an important aspect when considering it in the treatment of endometriosis since it can reduce muscle spasms, lessen menstrual bleeding and inflammation, thereby reducing congestion. The mild oestrogen modulating action, possibly due to the sterol and saponin content is often employed in treatment strategies that are directed at lowering menstrual pain and in order to help in the regulation of bleeding during normal menstruation in women. To date no studies have been conducted on the effects of Calendula officinalis on women with endometriosis. Others have suggested that calendula may relieve inflammation and improve immunity by blocking certain inflammatory compounds and limit the infiltration of white blood cells [52]. It could be proposed that calendula may help improve the dysregulation of the immune system in endometriosis (by decreasing the recruitment of white blood cells to inflamed regions), thus preventing the growth and spread of ectopic endometrium.

Cinnamon (*Cinnamomum zeylanicum*)

Actions Include: Warming circulatory stimulant, Anti inflammatory, Anti microbial, Spasmolytic Vulnerary Cinnamon is traditional used as a warming expectorant in respiratory condition, whilst cinnamon cassia is used to regulate blood sugar levels, and thus has application for diabetes [54]. A range of *in vivo* studies have demonstrated the anti-inflammatory actions of cinnamon, with its activity attributed to eugenol [48,55]. A dry 90%-ethanolic extract produced dose-dependent wound-healing effects, promoting all the crucial phases of healing (collagenation, wound contraction and epithelialisation), when administered orally at 250 or 500mg/kg daily *in vivo* [56]. Due to the actions of cinnamon it is also indicated for blood stasis or 'cold period pain' and cramping and has the ability to move blood flow through the pelvic region [36]. Cinnamons effects on blood flow and blood stasis make it an important consideration for the treatment of endometriosis. Interestingly, cinnamon has been shown to decrease the recruitment of macrophages in chronic inflammatory conditions such as atherosclerosis [57]. It raises a possibility that cinnamon can also reduce macrophage recruitment in other chronic conditions such as endometriosis.

Black cohosh (*Cimicifuga racemosa*)

Actions Include: Uterine tonic, Anti inflammatory, Emmenagogue, Analgesic.

The plant's anti-inflammatory and analgesic properties are attributed to its aromatic acids, which appear to inhibit prostaglandin production [36]. The roots and rhizomes are used in herbal treatments with the main active components being Actein, Cimifugoside and alkaloids. These components of this herb are beneficial in reducing dysmenorrhoea symptoms that are common in endometriosis. The herb is also useful for dull aching quality pain of the bowels (often associated with endometriosis), and dragging uterine pain which may be associated with adhesions and scarring caused by endometriosis [41].

Dong quai (*Angelica sinensis root*)

Actions Include: Antispasmodic, Anti-inflammatory, Immune-modulator, Analgesic, Warming uterine circulatory stimulant

Administered in a fluid extract for 1 week prior to menstruation has been shown a reduction of menstrual pain and inflammation of the endometrium [58]. Its anti-inflammatory inhibitory effect on prostaglandin thromboxane A2 synthesis *in vitro* [58] is also believed to provide an analgesic effect. The pharmacological basis for use of dong quai for dysmenorrheoa is believed to be due to its effects on uterine smooth muscle [59]. *In vivo* experiments have demonstrated increased excitability on the uterus, where the contractive rhythm of uterine smooth muscle changed from fast, weak, and irregular to slower stronger, and more coordinated (more rhythmic), depending on uterine tone. The volatile oil constituents, such as ligustilide, butylidenephthalide, and butylphthalide found to exert non-specific antispasmodic activity against rat uterine contractions and in other smooth muscle systems. Water-soluble, non-volatile constituents of the herb provide an opposite uterine stimulating effect [41,60].

Pulsatilla/Pasque flower (*Anemone pulsatilla*)

Actions Include: Warming diaphoretic, Anti-inflammatory, Emmenagogue, Anti spasmodic, Analgesic.

Sedative Many inflammatory conditions of the genitourinary tract such as interstitial cystitis and 'frequent but ineffectual attempts at urination [and], the bladder giving a sensation as if it is bloated', which are often associated with endometriosis, which may be alleviated with this herb. Is a warming emmenagogue herb with a cooling potential and is listed in the British Herbal Compendium [61] for painful and spasmodic condition of the uterus such as dysmenorrhoea. This herb has analgesic and sedative properties. Smaller doses with these patients will produce better results [62].

Ginger root (*Zingiber officinale*)

Actions Include: Anti-inflammatory, Analgesic, Antispasmodic, Anti-prostaglandin, Circulatory stimulant, Cholagogue, Inhibits synthesis of prostaglandins More than 100 compounds have been reported, some of which are isolated and characterized, others are tentatively identified by GC-MS and / or LC-MS. [6] Gingerol, the major gingerol in the rhizomes, has been found to possess many interesting pharmacological and physiological activities, such as anti-inflammatory and analgesic effects.

The squeezed ginger extract augmented the production of tumor necrosis factor-α, interleukin-6, and monocyte chemotactic protein-1 when added to RAW 264 cells [63]. By inhibiting these inflammatory properties it is possible to reduce the inflammatory nature of endometriosis and possible reduce the formation of lesions and the recruitment of activated macrophages.

Its warming properties (hot in the 1st degree) make it useful for gynaecological pain that improves with the application of heat. This herb also stimulates peripheral blood flow. Its analgesic effects are due to the herb's pungent action and possibly via its prostaglandin-inhibition action. The antispasmolytic actions of this herb are not just important for reducing pain in the uterus but also for other tissue including the intestine, bowel and kidneys.

White peony/paeonia/bai shao (*Paeonia lactiflora*)

Actions Include: Hormonal modulator, Progesterogenic, Immune modulator, Anti-inflammatory, Anti spasmodic, Uterine Tonic.

Administration of a traditional Oriental herbal prescription containing Paeonia gradually decreased tissue-specific anti-endometrial IgM antibody levels in patients with endometriosis. (Other constituents, all in equal amounts, included Paeonia suffruticosa, Poria cocos, Prunus persica and Cinnamomum cassia.) [64]. The root contains a monoterpene glycoside which is its main constituent called paeoniflorin which may play a role in its anti-inflammatory activity and antispasmoic activity on smooth uterine muscle [65]. *In vitro* experiments showed that paeoniflorin affected the ovarian follicles through its action on aromatase enzyme. Although, there is conflicting research, Peony may also normalise oestrogen/progesterone balance. An *in vitro* study found that incubation of ovary cells with Paeonia resulted in elevated progesterone secretions [66]. Oestrogen excess in relation to progesterone also responds well to Peonia containing formulations. A formula containing Paeonia lactiflora and suffruticosa, as well as Cinnamomum cassia, Prunus persica (Peach kernels) and Poria cocos (hoelen) may act as a weak anti-oestrogen by competing with oestrogen in uterine or breast tissue [67].

Schisandra (*Schisandra chinensis*)

Schizandra also have adaptogenic and nervine tonic actions, which will help the stress and intense feelings the client is having around her periods. Improving the clearance of oestrogen is particularly beneficial in oestrogen dominance related to PMS symptoms. Schizandra aids in the removal of oestrogen from the body to prevent recirculation and build up by acting on improving phase I and II liver detoxification pathways [44]. Research has shown that schisandra has anti-inflammatory constituents that could be beneficial in endometriosis. The α-cubebenoate constituent has been shown to inhibit the expression of iNOS and COX-2 [68]. Thereby supressing the production of nitric oxide and PGE2 – thus making it relevant to the treatment of endometriosis.

Feverfew (*Tanacetum parthenium*)

Actions Include: Anti-inflammatory, Anti prostaglandin.

Romm has provided an argument to support the use of this herb due to its anti-inflammatory actions. This herb inhibits prostaglandin synthetase which prevents the conversion of arachidonic acid to inflammatory prostaglandins (described above). This herb has been shown to reduce other inflammatory mediators that have been reported to be abnormal in endometriosis and include TNF-α, IL-1 and INF-γ together with a reduction in peritoneal cyclooxygenase [41].

Gotu kola

Actions Include: Anti-inflammatory, Antioxidant, Antimicrobial, Anti-fibrotic, Anti-proliferative, Vulnerary.

This herb has anti-inflammatory, antimicrobial, anti-fibrotic, anti-proliferative and antioxidant actions. These herbal actions make this herb quite unique in its ability to resolve and prevent the formation of keloid scars [36]. This herb can also be considered as a primary treatment protocol after surgical intervention to reduce adhesion and scar formation. This same line of approach can be considered for treatment of endometriosis to prevent further adhesions forming.

Echinacea species

Actions Include: Immune stimulant, Lymphatic cleanser, Anti microbial, NK stimulant.

To date there are no human studies on the effects of Echinacea on women with endometriosis and their impact on the immune system. A number of extrapolations can be made from others studies that show a benefit of Echinacea on the immune system through increasing the number and activity of natural killer cells [69]. *In vitro* studies show that Echinacea extracts are potent activators of NK cytotoxicity and the secretion of cytokine IFN-γ [69]. Since natural killer cells are reduced in woman with endometriosis it is possible that Echinacea may be of benefit to help rectify the reduced number and activity of these cells. Furthermore the oral ingestion of Echinacea *in vivo* has exerted a strong inhibition of products secreted by macrophages, including TNF-α and IL-1 69]. Extrapolating from this study, Echinacea may have beneficial effects by reducing the cytokines (TNF- and IK-1) thus decreasing the inflammatory drive in endometriosis.

This review has highlighted that there are a range of herbs that have the capacity to improve immunological function in endometriosis, in particular the cellular immunity patterns. Herbal medicines have been shown to mitigate the inflammatory overdrive in endometriosis, which is a key treatment consideration. A range of herbs have been shown to reduce macrophage recruitment into endometrial lesions, and thus potentially reduce the ongoing potential of endometriosis to evade further into the peritoneum. This mechanisms is mediated by reducing the products that macrophages synthesis, including TNF-α and IL-1. Improving immunological surveillance (through increasing cytotoxicity of NK cells) has been achieved with herbs, such as Echinacea. This mechanism could reduce the ability of retrograde endometrial cells to take up residence in the peritoneum. Other herbs have been shown to reduce oestrogen concentration by indirectly improving liver function (herbs include turmeric and schisandra). Further to this there are herbs that promote lymphatic clearance, which plays an important role in lessening menstrual blood, inflammation and congestion – all important treatment aspects for endometriosis. Thus the benefits of herbal medicine should be taken into account for the treatment of the range of symptoms women experience with endometriosis.

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