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Green Tea for Endometriosis

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1. Introduction

Endometriosis is a common gynaecological disease, defined by the presence of endometrial tissue outside the uterus, causing pain and infertility of women in reproductive age (Galle, 1989). It is estimated that it occurs in 10-15% for women in the reproductive age and more than 30% of all infertile women are affected (Cramer *et al.*, 2002). However, the actual figure on the total prevalence may even be higher, as the disease is often not diagnosed due to heterogenous clinical manifestations. These manifestations include dysmenorrhoea, dyspareunia, dysuria and chronic abdominal or pelvic pain as well as infertility, resulting in a severely limited quality of life (Davis *et al.*, 2003; Milingos *et al.*, 2006; Vercellini *et al.*, 2007). Thus, the aim on treating endometriosis should ideally target the endometriosis itself, i.e. relieves pain, promotes fertility and prevents reocurrence. Unfortunately, there is no current treatment being able to fulfill all these requirements. All conservative treatments, either medical or surgical, are still liable for disease reocurrence, and they do not address the cause and possible side effects brought upon to the disease mechanism and the patient outcomes.

In this chapter, we will analyze the rationale and limitations of the current therapy of endometriosis. Also, we will discuss on the latest therapies that hold a higher efficacy and sensitivity on treating the disease. Most importantly, we will highlight the effect of green tea on being a potential remedy toward tackling endometriosis.

1.1 Current and new treatment

In the past, the disease was best thought to be treated surgically. And with the advancement of operative laparoscopy, the treatment of endometriosis could be started as soon as it was diagnosis. However, different researches have shown surgical removal of endometriosis can bought upon many complications and chronicity. Likewise, without medical supplements, the patients would have a high chance for disease reocurrence. Hence, there is a great demand for medical treatments that can induce a suppression of this disease.

The type of treatments offer would depend on the extent or stage of the disease, the amount of pain suffered, and fertility wanted (Valle *et al.*, 2003) (Fig. 1). To perform the best therapy would require complete diagnosis and inspections of the lesion to determine the symptoms and staging of the patient's endometriosis (Olive *et al.*, 2001). The choices of present treatments include expectant management, medical therapy and surgical treatment (Table 1).

Traditional treatment
Expectant Management
Medical Therapy
- Analgesics
- Hormonal
- Selective progesterone receptor modulators
- Selective estrogen receptor beta agonists
- Gonadotropin releasing hormone antagonists
Surgical Treatment
- Conservative Surgery
- Definitive Surgery

New treatment
Angiogenesis inhibitors
Antioxidant therapy
Aromatase inhibitors
Tumor necrosis factor-alpha inhibitors
Matrix metalloproteinase inhibitors
Immunomodulators
Traditional Chinese medicines

Table 1. Treatment of Endometriosis

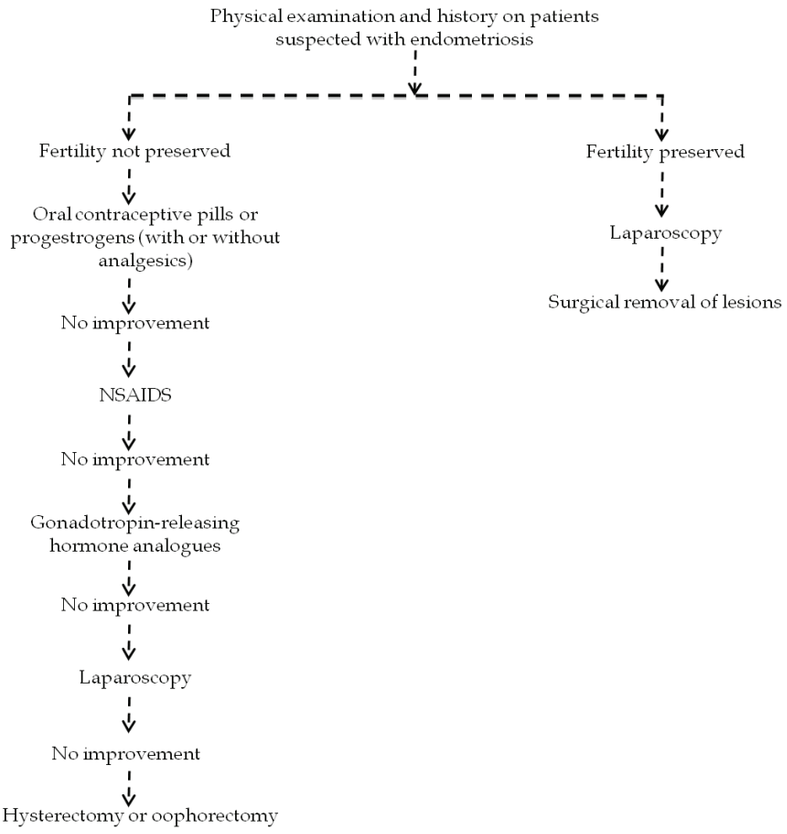

Fig. 1. Clinical evaluation on patients with endometriosis

1.1.1 Expectant management

In asymptomatic patients, those with mild symptoms or infertility with minimal endometriosis, expectant management may be prescribed. These women may opt for birth control pills because they can prevent endometriosis from progressing and protect against unwanted pregnancy (Bedaiwy *et al*., 2009). While for women approaching the menopause, they may also be managed expectantly, because the growth of endometriosis is suppressed after the menopause.

1.1.2 Medical therapy

Medical therapies are typically used for patients with endometriosis that have minimal pelvic pain. The types of medical therapies can be divided into two main categories: analgesics and hormonal. However, medical therapy alone is not appropriate for women with more advanced stages of endometriosis or those desiring pregnancy. And unlike surgery, medical therapy does not enhance your chances of conception (Hansen *et al*., 2006).

1.1.2.1 Analgesics

Analgesics treatments are often the first-line therapy in women with primary dysmenorrhea or pelvic pain and those with minimal pain symptoms associated with endometriosis. For mild cases of endometriosis, analgesic medications alone may be sufficient to relieve symptoms (Mahutte *et al*., 2003). Commonly used analgesic medications include paracetamol and non-steroidal anti-inflammatory drugs (NSAID). Although the use of analgesic treatments for pain relief is regularly prescribed, lack of clinical studies have critically evaluated their effectiveness.

1.1.2.2 Hormonal

Hormonal treatments are aimed at decreasing the amount of estrogen in the body, which will inhibit the progression of the endometrial implants (Coutinho, 1982). The most common hormonal medications used are combined oral contraceptives, progestins, androgens, and gonadotropin-releasing hormone (GnRH) agonist analogs. Combined oral contraceptives has been used for women with endometriosis since the 1950s (Kistner, 1959). These pills consist of a low combination of synthetic estrogen and progesterone. They have been shown to be very effective for patients with mild symptoms of endometriosis (Vercellini *et al*., 1993; Vessey *et al*., 1993). The main advantages are that it is inexpensive and is usually reasonably well tolerated by women (Kennedy, 2004). It can also be taken safely for many years if necessary (Kennedy, 2004). However, it is not free of side effects. These include irregular vaginal bleeding, fluid retention, abdominal bloating, weight gain, increased appetite, nausea, headaches, breast tenderness and depression.

Progestins are a group of drugs that behave like the female hormone progesterone. Although the actual mechanism on how progestins relieve the symptoms of endometriosis remained unclear, a possible effect might be the growth of endometrial implants was suppressed by this hormone, causing them to gradually regress (Schweppe, 2001). Other reported that they may reduce endometriosis-induced inflammation in the pelvic cavity (Vercellini *et al*., 2003). In clinical trials, it showed progestins being effective treatments for the symptoms of endometriosis (Kennedy *et al*., 2005). When taken continuously daily, they have shown to relieve endometriosis-associated pain as effectively as the other hormonal drugs (Kennedy *et al*., 2005). However, there are side effects, which include irregular menstrual cycle, sore breasts,

headache, nausea, dizziness and bloating. These side effects are not usually serious and long-lasting (Winkel *et al.*, 2001), however many patients still feel unpleasant and difficult to cope with. Hence, most women could seldom complete this type of treatment.

Danazol is an effective androgen for treating endometriosis. It works by suppressing the growth and development of the endometriotic lesion temporarily, hence continuous medication is required. Clinical trials have shown that danazol is effective in relieving the pain symptoms of endometriosis (Kennedy *et al.*, 2005) for approximately 90% of women (Biberoglu *et al.*, 1981). However, common side effects from these treatments include acne, oily skin, increased hair growth, and weight gain. Its unpleasant side effects and its risk of developing cardiovascular disease mean it is not the first choice of treatment for endometriosis (Kennedy, 2004).

Gonadotropin releasing hormone (GnRH) agonists are a group of drugs that have been used to treat women with endometriosis for many years (Schweppe, 2005). They work by stopping the production of estrogen by a series of inhibition on the estrogen-related pathway mechanisms. Although this treatment can reduce 50% in symptoms, but in long-term, pain recurrence can be observed in up to 75% of the cases (Surrey *et al.*, 2002). Likewise, affecting the estrogen hormonal cycle can result in major side effects like bone thinning (Pierce *et al.*, 2000).

1.1.3 Surgical treatment

Typically surgery becomes a choice after expectant management and hormonal therapy failed to reduce the patient symptoms (Olive et al., 2001; Winkel et al., 2001). Likewise, when anatomic distortions due to endometrial growths are present, surgery would also be the primary choice for treatment (Surrey *et al.*, 2003). There are mainly two types of surgery associated with endometriosis: conservative and definitive.

1.1.3.1 Conservative surgery

This type of surgery is employed in cases of mild to moderate endometriosis, and for women who would like to retain fertility, as this surgery saves as much ovarian tissue and uterus as possible (Camanni *et al.*). The most common conservative surgical approach is the use of laparoscopy for treating endometriosis (Brosens *et al.*, 1981). The aim of this type of surgery is restoration of the normal anatomy of the pelvis. Clinically, it has been shown that most patients, who undergone conservative surgery, realize a relief of pain symptoms associated with endometriosis. Women who had their implants excised had fewer symptoms 12 months (Abbott *et al.*, 2004) and 18 months (Sutton *et al.*, 1994; Sutton *et al.*, 1997) after surgery compared with women who underwent a laparoscopy without excision of their implants, respectively. However, this type of surgery has a high reoccurrence rate of up to 40% at 10 years post surgery.

1.1.3.2 Definitive surgery

On the other hand, patients suffering from painful symptoms resulted from severe endometriosis, and when fertility does not need to be retained, may require definitive surgery. This can involves the removal of the uterus (hysterectomy), fallopian tubes (salpingectomy), deep endometrial implants (debulking) and scar tissue (fibrinolysis). The ovaries may also be removed (oophorectomy) to prevent fluctuation of estrogen levels, which may cause any remaining endometrial implants to continue to grow. In such cases,

estrogen medication would be given to prevent menopausal symptoms to occur in the patients. Likewise, woman who underwent oophorectomy for endometriosis has greater pain relief and less likelihood of repeated surgery than those operated by hysterectomy with ovarian preservation (Namnoum *et al.*, 1995). In addition, the rate of recurrence in patients with definitive surgery is much lower than in those with conservative surgery.

1.1.4 Latest treatments developed against endometriosis

Recently, with the better understanding on the pathogenesis and progression toward endometriosis, novel medications on using molecular targets are developed for treatment of endometriosis. The advantages of such agents hold a higher efficacy and sensitivity on treating the disease, while minimizing evidence of side effects experienced by the patients.

1.1.4.1 Anti-angiogenesis inhibitors

One of the main etiologies of endometriosis is believe to be resulted from implantation of retrograde shed endometrium during menstruation (Sampson, 1927). The properties of the endometrium have the capacity to adhere, attach, and implant ectopically (Koks *et al.*, 1999; Maas *et al.*, 2001). Based on the anatomical surrounding, endometriotic lesions are found to be larger in size with the availability to rich blood supply. This suggesting that angiogenesis is prerequisite for the development of endometriosis.

The use of angiostatic agents may provide a new therapeutic option to inhibit this pathological process. The aim is to mainly control two processes involved in angiogenesis: endothelial cell growth and endothelial cell adhesion. Angiogenic cytokines are elevated in the peritoneal fluid in patients with endometriosis (Nisolle *et al.*, 1993). Anti-angiogenesis therapies have been shown effective in suppressing the development in endometriotic lesion in mice (Nap *et al.*, 2004). Common angiostatic compounds, such as anti-human vascular endothelial growth factor-A (anti-hVEGF), TNP-470, endostatin, and anginex, significantly decreased microvessel density and inhibited the established endometriosis lesions (Dabrosin *et al.*, 2002; Nap *et al.*, 2004; Yagyu *et al.*, 2005). By far, the only clinical trial conducted with an anti-angiogenesis therapy on treating endometriosis-associated pain was thalidomide (Scarpellini *et al.*, 2002). Although the result showed promising pain relief in the patients, however, thalidomide is a potential teratogen (Khoury *et al.*, 1987). Thus, women wanting pregnancy is prohibited.

1.1.4.2 Anti-oxidant therapy

Although the actual etiology of endometriosis remains unknown, it is widely accepted that retrograde menstruation is associated with endometriosis. However, it is unclear on why only a portion of women with retrograde menstruation develops endometriosis, while others do not. Studies proposed this might be due to the presence of elements such as macrophages, iron or environmental contaminants disrupting the balance between ROS and antioxidants in the peritoneal fluid of some women, leading to oxidative stress and endometriosis (Arumugam *et al.*, 1995; Donnez *et al.*, 2002; Murphy *et al.*, 1998). Likewise, the cyclical changes in the endometrium are accompanied by changes in the expression of various antioxidant enzymes in the endometrium (Gurdol *et al.*, 1997).

Patients with endometriosis have shown the increase in generation of ROS by peritoneal fluid macrophages, with increased lipid peroxidation (Halme *et al.*, 1983). The diminished peritoneal fluid antioxidants (Murphy *et al.*, 1998), elevated oxidized lipoproteins, lysophosphatidyl choline (Murphy *et al.*, 1998), and other markers of lipid peroxidation

provide further evidence of oxidative stress in the peritoneal microenvironment of endometriosis (Ho *et al.*, 1997; Szczepanska *et al.*, 2003).

Currently, a study investigated whether there would be reduced total chemokines and inflammatory cytokines in women with endometriosis (Santanam *et al.*, 2003). As patients were given 1200 IU of vitamin E and 1 g of vitamin C for a period of 2 months, this resulted in a decrease in the inflammatory markers monocyte chemotactic protein-1, regulated on activation normal T cell expressed and secreted (RANTES), and interleukin-6 in peritoneal fluid. Similar study showed these antioxidant supplements can reduce pelvic pain in women with endometriosis (Kavtaradze *et al.*, 2003).

Recently, an inhibitory drug has been used in clinical trials to determine the effect of anti-oxidant therapy on endometriosis (Creus *et al.*, 2008). Pentoxifylline, a phosphodiesterase inhibitor, has the capability to maintain a higher pregnancy rates in patients suffering from endometriosis. RU 486 exerts an inhibitory effect on endometrial cell growth through its antioxidant properties *in vitro*. Although antioxidants have shown to have beneficial effects in patients with endometriosis, the limited number of trials conducted questions the actual efficacy.

1.1.4.3 Hormone inhibitors and modulators

As endometriosis is an estrogen-dependent disease, the estrogen-related pathways are often the treatment used to tackle the imbalanced of estrogen in these female patients. A way is to suppress the production of estrogen by inhibiting its synthetic and regulatory pathway. Another potential way is to influence estrogen receptors minimizing estrogen-dependent gene expressions.

Since aromatase, the key enzyme in estrogen synthesis in ovary, adipose tissue or endometriotic tissue, is encoded by a single gene, the inhibition of this gene or its production may cause an effective suppression of estrogen production (Simpson *et al.*, 2002). Preliminary evidence suggests that combined treatment with luteinizing-hormone-releasing hormone analogues and aromatase inhibitors may be superior to medical treatment with luteinizing-hormone-releasing hormone analogues (Shaw, 1988).

Another type of treatment is by using tumor necrosis factor alpha (TNF-α) inhibitor. This cytokine have been found to be overproduced in women with endometriosis, and partially responsible for the influx of peritoneal macrophages to occur in women with endometriosis (Montagna *et al.*, 2008; Richter *et al.*, 2005). A study was conducted to see the therapeutic effect on blocking this cytokine with recombinant human TNF binding protein-1 (TBP-1) in a baboon model (D'Hooghe *et al.*, 2005). The result demonstrated the inhibition in the baboon, suggesting the effective in treating the manifestations of endometriosis. However, there is currently no clinical study to determine the effect in human.

1.1.4.4 Proteases

Matrix metalloproteinases (MMPs) are a family of endopeptidases that play a role in the degradation and turnover of extracellular matrix proteins. Increased MMP activity has been described in endometriosis (Chung *et al.*, 2002; Gottschalk *et al.*, 2000). There function is believed to be integral in the ability of endometrium to invade tissue and implant successfully. Inhibition of these enzymes might be effective in inhibiting the development of endometriosis. Yet, there is no in-depth study being reported thus raising uncertainty on the value and practicality of this approach.

1.1.4.5 Traditional Chinese medicines

As surgical and hormonal treatment of endometriosis have unpleasant side effects and high rates of relapse, many patients began to explore more natural and traditional remedies. In China, treatment of endometriosis using Chinese herbal medicine is routine to alleviate pain, promote fertility, and prevent relapse. Study showed post-surgical administration of Chinese herbal medicine may have comparable benefits to western medicines but with fewer side effects (Flower *et al.*, 2009). In this study, it showed oral intake of traditional Chinese medicine have a better overall treatment effect than Danazol. Also, it is more effective in relieving dysmenorrheal and shrinking adnexal masses. Likewise, acupuncture is a new techniques employed to relieve the infertility associated with endometriosis in women (Mo *et al.*, 1993). However, due to the limited amount intervention studies reported, more rigorous researches are required to accurately assess the type, dose and potential role of Chinese herbal medicine in treating endometriosis.

2. Anti-angiogenesis therapy

2.1 Properties of anti-angiogenesis therapy

Angiogenesis is the physiological process involving the growth of new blood vessels from pre-existing vessels. It is a sequence of events that is fundamental to a broad array of physiological processes occurring in our body, including embryogenesis, development, the menstrual cycle and wound healing. Yet, it is also linked to many pathological situations such as cancer, chronic inflammation, ischemic diseases and endometriosis development (Griffioen *et al.*, 2000). In general, the turnover of capillary endothelial cells is extremely slow in physiological angiogenesis. However, in the normal endometrium and in tumors, the turnover rate is altered to a more rapid state in promoting angiogenesis. Angiogenesis involve activation of angiogenic factors, dissolution of basement membranes by proteases derived from vascular endothelial cells, migration and proliferation of the endothelial cells, and capillary tube formation. And various angiogenic factors are needed to regulate each step (Table 2).

Under normal physiological conditions, angiogenesis is well controlled by the local balance between endogenous angiogenesis stimulators and angiogenesis inhibitors, although the regulatory mechanism is still not clear. During wound healing, the expression of vascular endothelial growth factor (VEGF), one of the most potent angiogenic stimulators, is significantly upregulated to promote wound healing by restoring blood flow to the injured tissues. As wound healing resolves, the expression of VEGF is downregulated and most angiogenic capillaries regress, resulting in a residual normal vascularity (Tonnesen *et al.*, 2000). Other studies indicates that a number of endogenous angiogenic inhibitors are present in the normal retina to balance the stimulatory effect of VEGF in the regulation of angiogenesis and vascular permeability (Ma *et al.*, 2005). These studies suggest that endogenous angiogenic inhibitors can be used to balance the effect of angiogenic stimulators. Anti-angiogenic therapies have already been experimentally proven to be effective in preventing metastasis and shrinking the established experimental tumors to be formed (Camp-Sorrell, 2003). Angiogenesis therapeutic approaches can be divided into two major classes: (1) interference with the process of neovascularization and (2) directly destroying immature blood vessels.

Interleukin-1
Interleukin-6
Interleukin-8
Epidermal growth factor
Basic fibroblast growth factors
Insulin-like growth factors
Platelet-derived growth factor
Platelet-derived endothelial cell growth factor
Vascular endothelial growth factor
Endometriosis protein-I
Ovarian steroids
Estradiol
Angiogenin
Proliferin
Pleiotropin
Tumor necrosis factor-α
Hepatocyte growth factor
Transforming growth factor -α and -β
Placenta growth factor

Table 2. Angiogenic factors in endometriosis

Although they may not necessarily directly kill tumor cells, angiogenesis inhibitors significantly enhance the efficacy of standard chemotherapy and radiation therapy by inhibiting tumor growth and tumor metastasis. Therefore, this type of therapy may need to be administered over a long period of time. In the normal healthy body, the process of angiogenesis is dormant and the angiogenesis switch is kept "off" with inhibitors being dominant over stimulators. Since anti-angiogenesis therapy is a targeted therapy aimed specifically at the angiogenic stimulators and the angiogenic microvascular endothelial cells, anti-angiogenesis therapy usually produces only mild side effects and is less toxic to most healthy cells. But as physiological angiogenesis is important in wound healing and reproduction, bleeding, blood clotting, heart function, the immune system, and the reproductive system, the unknown consequences on long-term treatment with anti-angiogenic agents would still be a great concern (Board *et al.*, 2006; Cabebe *et al.*, 2007).

2.2 Anti-angiogenesis potentials for endometriosis

To date, endometriosis is often treated by hormonal medication, which aims at achieving a hypoestrogenic state. However, hormonal therapy would only suppress the symptoms associated with endometriosis, but not eradicating the ectopic implant. Moreover, significant side effects hinder the continuation of treatment (Saltiel *et al.*, 1991). Long-term hormonal therapy, therefore, is not an attractive option. Alternatively, endometriosis can also be treated surgically. Conservative surgery consists of ablation of endometriosis lesions, resulting in pain relief, but high symptoms recurrence has been reported in a majority of patients (Vercellini *et al.*, 2009). While definitive surgery includes removal of uterus, with or without ovaries, giving more permanent symptom relief, this therapy would result in the end of reproductive life. Therefore, an effective therapeutic agent for endometriosis would be a compound that not only prevents the development of endometriosis lesions, but would also be effective against the growth of established lesions. In cancer, endothelial cells have been shown to play a pivotal role in tumor cell survival and growth. In analogy with tumor

growth, endometriosis is shown to be highly dependent on angiogenesis, which makes the achievements in the field of cancer research applicable to endometriosis.

Most of the studies on the role of angiogenesis in endometriosis have been performed in animal models so far. Still, more experiments are urgently needed to distinguish the effect of angiogenesis inhibitors on physiological and pathological angiogenesis. Like in a recently published study, the effect of angiogenesis inhibition was studied in nude mice. VEGF-A inhibitors were administered immediately after implantation of cultured human endometrium fragments (Hull *et al*., 2003). The results showed impaired lesion formation, which concluded that angiostatic agents may be effective in the treatment of endometriosis. And recently, encouraging results have been achieved with the use of Avastin, a humanized anti-VEGF antibody, on cancer. This approach of neutralizing VEGF provided the first proof of concept that anti-angiogenesis is applicable in humans (Ferrara, 2002; McCarthy, 2003). Yet, it still needs clinical trial to make a more concrete result on the anti-angiogenesis effect. With prior to clinical testing to commence, the optimal mode of delivery and the best indication of anti-angiogenic therapy would still need to be determined. However, the encouraging results of some anti-angiogenic drugs and the pressing need for new therapeutic approaches make angiogenesis an attractive novel target for the treatment of patients with endometriosis.

2.3 Limitations

The limitation of anti-angiogenesis therapy is that the patient's immune system may be compromised (Calabrese *et al*., 2000). This would make the patient more susceptible to infection and delay wounds healing. In addition, patients may experience reproductive problems and damage to the fetus, if the patient was pregnant while taking the anti-angiogenic drug. Other research has reported such therapy can enhance heart problems, elevating blood pressure and bleeding or blood clots could increase. Since angiogenesis inhibitor therapy is still under investigation, the definite possible complications and side effects are still unknown.

3. Green tea and its clinical values

3.1 Properties of green tea

Tea (*Camellia sinensis*) is an aromatic beverage prepared from boiling or simmering of cured leaves. Apart from water, tea is one of the most popular consumed beverages worldwide, with a consumption of 120mL/day/capita (Graham, 1992). Of the different varieties of tea, the most commonly found on the market are white, green, oolong and black tea. And over the last few decades, green tea has been subjected to many scientific and medical studies on its potential health beneficial effects (Table 3).

Anti-aging
Anti-bacterial
Anti-inflammatory
Anti-angiogenic
Anti-cancer
Lowering blood fat
Prevent tooth decay and clear bad breath
Enhanced skin whitening

Table 3. Benefits of green tea

Green tea contains polyphenols, particularly catechins, accounting for 30-40% of the dry weight (Balentine *et al.*, 1997; Graham, 1992). The main components of green tea consist of catechins, minor flavanols and polymeric flavonoids (de Mejia *et al.*, 2009). It contains more catechin concentrations than black tea or oolong tea, due to the minimal oxidation during processing. The compositions of green tea catechins are mainly comprised of (-)-epicathecin (EC), (-)-epigallocatechin (EGC), (-)-epigallocatechin gallate (EGCG), (-)-epicathecin gallatis (ECG), (-)-gallocatechin gallate (GCG), (-)-catechin gallate (CG) and (+)-cathecin (CT) (Miura *et al.*, 1994) (Fig. 2). Among the components of green tea, (-)-epigallocatechin gallate (EGCG) is the most abundant and the most extensively studied catechin, accounting to 50-80% of the total catechins in green tea (Yang *et al.*, 2002).

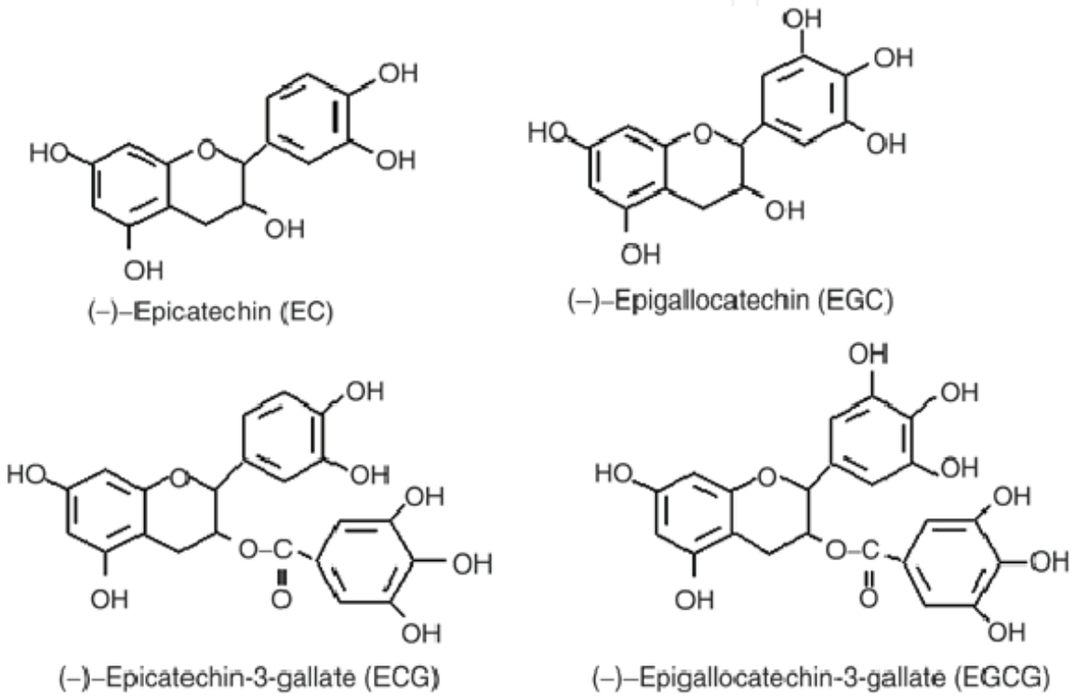

Fig. 2. The main catechins components found in green tea

3.2 Biological activities

3.2.1 Anti-oxidant activity

Free-radical damage has been postulated to contribute to the etiology of aging, and many chronic health problems such as cardiovascular, inflammatory diseases, and cancer (Rice-Evans *et al.*, 1993; Spiteller, 2001). The productions of free radicals, including reactive oxygen species (ROS), are capable of chemically altering many natural bio-molecules in our body, resulting in changes in their structure and function, leading to aging and the development of chronic diseases (McCall *et al.*, 1999).

Like most polyphenols, catechins and procyandins have an anti-oxidant activity. In a study conducted by Guo *et al*, ECG and EGCG displayed better antioxidant activity than EC and EGC on lipid peroxidation (Guo *et al.*, 1996). Also, green tea catechins have been shown to protect or regenerate α-tocopherol in human low-density lipo-protein (LDL), which

functions as a major antioxidant in human LDL (Zhu *et al*., 1999). Similarly, EGCG and EGC show potent inhibitory effects on LDL oxidation *in vitro*, with EC and ECG being even more effective on protective activity on the depletion of α-tocopherol in LDL. And a clinical study claimed the consumption of 300 mg of green tea polyphenol extract twice daily for 1week can delayed the oxidation of human LDL *ex vivo* (Miura *et al*., 2000).

3.2.2 Anti-mitotic

Proliferation and migration of endothelial cells are major events in the angiogenic process for the formation of endometriosis. Matrix metalloproteinase-2 is expressed abundantly in lesions and has been suggested to play a key role in the degradation of the basement membrane, thereby promoting migration of endothelial cells (Zempo *et al*., 1994). Green tea polyphenols can significantly reduced endothelial cells proliferation in a dose-dependent manner and caused the accumulation of cells in the G_1 phase without affecting cell viability (Kojima-Yuasa *et al*., 2003). In addition, EGCG suppressed endothelial cells proliferation and migration by inducing apoptosis through mitochondrial depolarization, activation of caspase-3 and reduction of binding of VEGF to its receptors in human ECs (Kondo *et al*., 2002; Yoo *et al*., 2002).

3.2.3 Anti-inflammatory

Cytokines are a group of multifunctional proteins that mediate the regulation of inflammatory responses. These cytokines are expressed in a number of tissues, including macrophages, vascular endothelial cells, adipose tissue and neurons. In general, the role of cytokines can be further classified depending on the way they influence inflammation, such as pro- or anti-inflammatory (Kundu *et al*., 2008). Factors such as tumor necrosis factor-α, IL-6, IL-1, GM-CSF, interferon-c, and IL-12 played a major role on the induction of the inflammatory response.

EGCG has been shown to possess anti-inflammatory properties *in vivo* and *in vitro* (Hamer *et al*., 2007). The potent effects of tea polyphenols toward inflammation have also been known to cancer prevention (Beltz *et al*., 2006). Tea polyphenols appear to modulate at different targets the anti-inflammatory activities related to arachidonic acid-dependent pathways, such as cyclooxygenase (COX) inhibition. Within the arachidonic acid-independent pathways, nitric-oxide synthase (NOS) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) are targets of polyphenols (Miles *et al*., 2005). The released phytochemicals inhibit cyclooxygenase-2 (COX-2) and inducible nitric-oxide synthase (iNOS) expression by blocking NF-κB activation. Particularly EGCG suppresses activation of NF-κB by repression of degradation of inhibitory unit, IκBκ, which hampers subsequent nuclear translocation of the functionally active subunit of NF-κB (Kundu *et al*., 2008).

3.2.4 Anti-angiogenic

It has been widely shown that green tea have the ability to inhibit angiogenesis in *in vitro* proliferation studies (Laschke *et al*., 2008; Park *et al*., 2006; Slivova *et al*., 2005) and in *in vivo* angiogenesis assays (Laschke *et al*., 2008; Xu *et al*., 2009). Anti-angiogenesis plays a crucial role accounting to the cancer-preventive effect made by green tea. As angiogenesis is a complex multi-step process that includes the proliferation, migration and differentiation of endothelial cells into tube-like structures. The initiation of each step involves multiple

growth factors, proteases and adhesion molecule secreted by the endothelial cells, as well as supporting cells from the surrounding (Carmeliet *et al.*, 2000). Pathogenesis related to abnormal angiogenesis can be demonstrated in rheumatoid arthritis, diabetic retinopathy, and cancer growth and metastasis. Therefore, angiogenesis would be a crucial process that may account for part of the mechanisms of the cancer preventive effect of green tea. Studies have shown green tea's potential to decrease vital angiogenic factors in breast cancer (Sartippour *et al.*, 2002; Sartippour *et al.*, 2002). Similarly, other showed the mark decrease of IL-8 production by endothelial cells (Tang *et al.*, 2001). Likewise, tumor necrosis factor-α and matrix metalloprotinases were suppressed by the incorporation of EGCG (Annabi *et al.*, 2002; Yang *et al.*, 1998). The observation on the effect of green tea being anti-angiogenic is clinically very significant (Kabbinavar *et al.*, 2003). With the lack of information on clinical trials, work is still needed on promoting green tea as a possible medication on anti-angiogenesis therapy.

3.3 Side effects of green tea

The preliminary efficacy results of a phase I–II clinical study from a cohort of non-cancer patients demonstrated no uncomfortable side effects (Choan *et al.*, 2005). To date, the only side effect reported from drinking green tea is to cause insomnia, increase heart rate and nausea in selected individual, due to the presence of caffeine. An average cup of tea (10 g of tea leaves in 1 L water) contains around 300 mg of crude solids with 30–42% catechins and 3–6% caffeine (Khan *et al.*, 2007). However, the amount of caffeine is three times less than that of drinking coffee. Thus, this makes drinking green tea a prospective and very safe treatment for clinical use.

4. Green tea for endometriosis

As already proven, the catechins, notably EGCG, found in green tea are potential candidates to inhibit the growth of tumors (Jung *et al.*, 2001; Nakachi *et al.*, 1998; Uesato *et al.*, 2001). They act as a pleiotropic substance, which influencing multiple mechanisms that are involved in carcinogenesis (Beltz *et al.*, 2006; Khan *et al.*, 2006) through suppressing angiogenesis (Kondo *et al.*, 2002; Zhu *et al.*, 2007). With these basic finding, recent direction pointed out that the anti-angiogenic and anti-oxidation properties of ECGC may be a promising therapeutic agent in treating endometriosis.

So far, there are two major groups studying the use of EGCG to relate with the inhibition of endometriosis (Laschke *et al.*, 2008; Xu *et al.*, 2009). In the study conducted by Laschke *et al.*, the study showed that EGCG suppresses E2-stimulated activation, proliferation and VEGF expression of endometrial cells *in vitro*. While in the *in vivo* study using dorsal skinfold chamber model, EGCG selectively inhibited angiogenesis and blood perfusion of endometriotic lesions. Similarly, histology of the endometriotic lesion revealed induced regression when EGCG was prescribed. The author proposed the possible mechanism on the inhibition on the growth of the lesion may be due to attenuation of VEGF expression by EGCG in cultured endothelial cells, with the stimulation with estrogen. This indicates that EGCG specifically blocks the E2-induced activation in endometrial cells, which EGCG would compete with E2 for binding to estrogen receptors. In addition, the study found that EGCG treatment may not only induce regression of endometriotic lesions, but may also have a positive anti-angiogenic effect on the eutopic endometrium of endometriosis patients. This was shown by the decrease in VEGF expression in the eutopic endometrium.

Likewise, the possible toxicity by EGCG toward the reproductive organs was also investigated. The treatment marked by EGCG showed no adverse effect neither on angiogenesis and blood perfusion nor tissue integrity of ovarian follicles.

In another study conducted by our team, we demonstrated the anti-angiogenic effects of green tea catechin on a mouse model induced with endometriosis (Xu *et al.*, 2009). These immunosuppressent mice were induced with endometriosis by subcutaneously implanting human endometrial tissues from patients with endometriosis. Following the day of operation, endometriosis induced mice were treated daily with saline, Vitamin E or EGCG for two weeks. The result showed those treated with EGCG, but not Vitamin E, have the smallest size of lesion growth. Angiogenesis in lesions from the implant and adjacent tissues was under-developed, and microvessel size and density were lower. With regards to the lower expression of VEGF expression, EGCG significantly inhibits the development of experimental endometriosis can be through anti-angiogenic effects. Following on this study, we investigate the likely mechanism would involve the selective inhibition of angiogenic factors, mainly VEGF-C/VEGFR2 pathway by EGCG to suppress the growth of the endometriotic lesions (Xu *et al.*, 2011) (Fig 3). With these studies, the potential of green tea as an anti-angiogenic agent is high because of its low cost, wide availability, and apparent low toxicity.

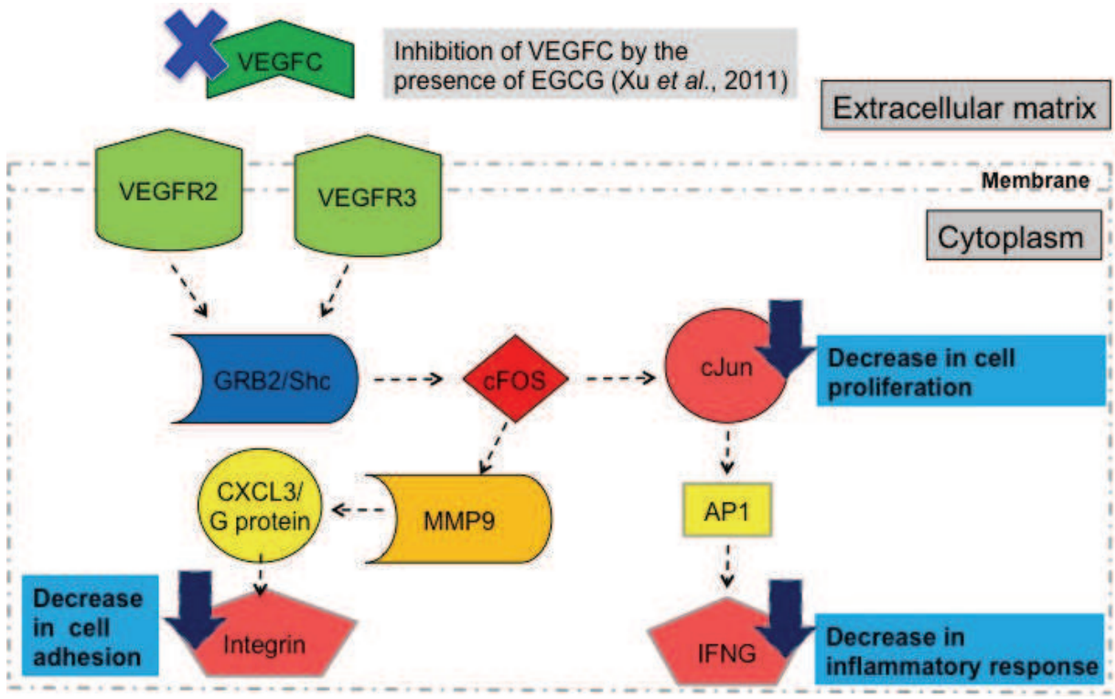

Fig. 3. Summary of the mechanism of green tea for endometriosis

5. Conclusion

Endometriosis is one of the most common benign gynaecological conditions. It affects an estimated 176 million worldwide regardless to their ethnics and social background. And it is estimated that 30-40% of women with endometriosis may not be able to have children. However, there is currently no single etiology that can explain the pathogenesis and pleomorphic manifestations of endometriosis.

Current treatments for endometriosis remain unsatisfactory, owing to their focus on treating the symptoms rather than curing the disease. In addition, each treatment proved to have many side effects (Rice, 2002). Hence, there is a need to derive a new therapy to provide a more efficient and specific therapeutic alternatives to eliminate the lesions, while preventing reoccurrence and retaining fertility.

To provide additional evidence to support the role of green tea in suppressing endometriosis, it would be an important future research goal. Several study areas should be emphasized. These areas include a more detailed molecular and cellular mechanism studies in animals and humans to verify the effects of green tea in humans, compared with those studied in animals. Next, the interactions between the green tea polyphenols and endometriosis have not been extensively investigated. This drawback can cause many important details being vague. Furthermore, the potential interactions of active compounds in green tea with other dietary active components and the roles of polymorphisms on the protective effects of tea need to be examined in future studies. Ultimately, clinical intervention trials should be conducted to verify the mechanisms of action of tea observed in animal studies in which tea does not show any unwanted side effect.

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7. Reference

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Endometriosis - Basic Concepts and Current Research Trends

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This book provides an insight into the emerging trends in pathogenesis, diagnosis and management of endometriosis. Key features of the book include overviews of endometriosis; endometrial angiogenesis, stem cells involvement, immunological and hormonal aspects related to the disease pathogenesis; recent research reports on infertility, endometrial receptivity, ovarian cancer and altered gene expression associated with endometriosis; various predictive markers, and imaging modalities including MRI and ultrasound for efficient diagnosis; as well as current non-hormonal and hormonal treatment strategies This book is expected to be a valuable resource for clinicians, scientists and students who would like to have an improved understanding of endometriosis and also appreciate recent research trends associated with this disease.

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