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Evolution of medical treatment for endometriosis: back to the roots?

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Experimental evidence is accumulating to suggest that medicinal botanicals have anti-inflammatory and pain-alleviating properties and hold promise for treatment of endometriosis. Herein, we present a systematic review of clinical and experimental data on the use of medicinal herbs in the treatment of endometriosis. Although there is a general lack of evidence from clinical studies on the potential efficacy of medicinal herbs for the treatment of endometriosis-associated symptoms, our review highlights the anti-inflammatory and pain-alleviating mechanisms of action of herbal remedies. Medicinal herbs and their active components exhibit cytokine-suppressive, COX-2-inhibiting, antioxidant, sedative and pain-alleviating properties. Each of these mechanisms of action would be predicted to have salutary effects in endometriosis. Better understanding of the mechanisms of action, toxicity and herb–herb and herb–drug interactions permits the optimization of design and execution of complementary alternative medicine trials for endometriosis-associated pain. A potential benefit of herbal therapy is the likelihood of synergistic interactions within individual or combinations of plants. In this sense, phytotherapies may be analogous to nutraceuticals or whole food nutrition. We encourage the development of herbal analogues and establishment of special, simplified registration procedures for certain medicinal products, particularly herbal derivates with a long tradition of safe use.

Keywords: endometriosis; herbs; botanicals; inflammation; CAM

Introduction

The successful treatment of endometriosis-associated symptoms including dysmenorrhoea, dyspareunia and chronic non-menstrual pain typically requires surgical as well medical intervention (Kennedy *et al*., 2005). The use of both general modalities for endometriosis-associated pain has been recently reviewed (Kennedy *et al*., 2005; Crosignani *et al*., 2006). The clinical prevalence of endometriosis symptomatology is very high. In a survey of reproductive-aged women in Canada, 60% met the criteria for primary dysmenorrhea (Burnett *et al*., 2005). In adult women with endometriosis, the prevalence rate of dysmenorrhoea was up to 76% (Kuohung *et al*., 2002), and in adolescents with endometriosis, it was up to 94% (Reese *et al*., 1996). This disease constitutes a public health dilemma of major proportion. Although medical therapies are not curative *per se*, they are nonetheless a mainstay of pain symptom suppression among women with endometriosis.

Initially high-dose diethylstilbestrol and combinations of potent estrogens and progestagens were used to treat endometriosis (Hurxthal and Smith, 1952), but this approach was subsequently replaced by progestagens alone (Kistner, 1958). In 1958, the clinical observation of an apparent resolution of symptoms during pregnancy gave rise to the concept of treating patients with pseudo-pregnancy hormone regimens (Kistner, 1958). Different forms of progestagens and anti-progestagens (including dihydrogesterone, medroxyprogesterone acetate (MPA), gestrinone and mifepristone (RU 486) afforded some improvement in pelvic pain; however, these treatments are ineffective in a subset of women with endometriosis and carry several untoward side effects (Vercellini *et al*., 1997). In 1973, danazol, a isoxazole derivative of 17-alpha testosterone, was introduced for the treatment of endometriosis-associated pain (Friedlander, 1973). Although danazol is effective, extended use is limited by androgenic and metabolic side effects (Selak *et al*., 2001). A decade later, in 1982, gonadotrophin releasing hormone agonists (GnRH-a) were first described as an alternative treatment for endometriosis (Lemay and Quesnel, 1982). Although GnRH-a can be used safely with combined estrogen and/or progestagen add-back therapy for up to 2 years, long-term use is constrained

by hypoestrogenic side effects (Corson and Bolognese, 1978), especially in adolescents.

Since 1978, non-hormonal treatment regimens for endometriosis-associated pain, including a variety of non-steroidal anti-inflammatory drugs (NSAIDs), have been promoted (Corson and Bolognese, 1978). Objective evidence on the use of NSAIDs in endometriosis-associated pain is sparse and inconclusive (Allen *et al*., 2005). Despite the poor quality of evidence, NSAIDs are typically used as first-line drugs in the treatment of endometriosis associated-pain, because they are felt to have fewer limitations (Allen *et al*., 2005).

Much effort is spent on the development and promotion of new drug treatments with the goal of achieving higher efficacy, fewer side effects and the option of long-term treatment, especially in women with severe endometriosis. These agents include thiazolidinediones (Lebovic *et al*., 2004), selective progesterone receptor modulators (SPRMs) (Chwalisz *et al*., 2005), aromatase inhibitors (Amsterdam *et al*., 2005), cyclooxygenase (COX)-2 selective NSAIDs (Cobellis *et al*., 2004), recombinant human TNF-alpha binding proteins (Barrier *et al*., 2004), anti-VEGF therapy (Nap *et al*., 2005), MMP-inhibitors (Mori *et al*., 2001) and interferon-alpha-2b (Badawy *et al*., 2001). Evidence from preclinical trials has suggested beneficial effects of these drugs that may be conferred by anti-proliferative, anti-inflammatory or anti-angiogenic mechanisms. However, despite these many therapeutic options, efficient long-term regimens for the treatment of endometriosis-associated symptoms are desperately needed.

In recent years, medicinal herbs and other botanical products have become popular for management of symptoms of several gynaecologic disorders (Eisenberg *et al*., 1998; Anderson and Johnson, 2005; Comar and Kirby, 2005; Tindle *et al*., 2005) including endometriosis-associated symptoms (Cox *et al*., 2003; Fugh-Berman and Kronenberg, 2003). Evidence for the potential efficacy of medicinal herbs in the treatment of endometriosis-associated symptoms has been reported in the literature and is the focus of this review.

Background

Traditional medicine practices refer to health approaches, knowledge and beliefs incorporating natural plant, animal and mineral-based medicines, spiritual therapies, manual techniques and exercises (Chen and Chen, 2004; Huang, 1998). These can be applied individually or in combination to treat and prevent illnesses or maintain well-being. In industrialized countries, adaptations of traditional medicine are termed complementary and alternative medicine (CAM). CAM is popular in all regions of the developing world and its use is rapidly spreading in industrialized countries. In Europe and North America, over 50% of the population have used CAM at least once (Tindle *et al*., 2005).

Historically, Chinese culture has relied heavily on herbal treatment of many illnesses. Traditional herbal preparations still account for 30–50% of the total medicinal consumption in China. Written records document the use of Chinese herbal medicine over 3000 years ago. In Chinese medicine, endometriosis is called Neiyi and is considered a 'Blood stasis syndrome' resulting in the formation of endometriotic lesions (Flaws, 1989; Maciocia, 1997). Chinese herbal formulae designed for endometriosis therapy are targeted to resolve blood stasis. Despite centuries of use abroad, medicinal herbal treatments for endometriosis-associated symptoms were only introduced in the USA in the mid-1980s. Several medicinal herbs that historically were prescribed for treatment of endometriosis-associated symptoms are still in use today (Chen and Chen, 2004; Huang, 1998) (Table 1). Each of the herbs described is likely composed of several active components with anti-inflammatory, anti-proliferative and pain-alleviating properties (Table 2). Thus, the potential for multiple synergistic interactions is enormous.

Clinical evidence on the efficacy, toxicity and herb–drug interactions of medicinal herbs and herbal combinations used in the treatment of endometriosis

We searched Medline (1969 to November 2006), EMBASE (1984 to April 2006) and hand searched several prominent journals published in China. Clinical evidence on the efficacy of herbal combinations in treatment of endometriosis is almost exclusively published in the Chinese scientific literature. As Chinese medicine traditionally uses mixtures of medicinal plants, synergistic as well as interfering effects may occur. The concept of synergistic interaction refers to the possibility that when two (or more) active substances are given concurrently, the substances may interact enhancing the effect of the other and at lower doses. Alternatively, multiple compounds could result in decreased efficacy. These possible interactions between two or more drugs/herbs are classified into pharmacokinetic and pharmacodynamic effects (Harrison and Fauci, 1998). Examples of medicinal herbal combinations that have been used to treat endometriosis-associated symptoms include: dan'e recipe, Gexia Zhuyu Tang, Keishi-bukuryo-gan (KBG), Neiyi recipe #1, Neiyi recipe #2, Neiyixiao recipe, Shixiao San (Sudden Smile Powder), Shaofu Zhuyu Tang, Shixiao Guijie Tang, Taoren Chenqi Tang, Tongjin San, Tuo Mo Tang, Tao He Cheng Tang, Xuefu Zhuyu Tang, Xiao Yao San, Yi Wei Zhu Yu Fang and Yiweining (YWN) (Shao, 1980; Cai, 1982; Dai, 1982; Cao, 1983; Liu *et al*., 1983; Lin *et al*., 1988; Zhuang and Xia, 1990; Jin, 1991; Li, 1991; Wang *et al*., 1991; Qu, 1992; Yu *et al*., 1993; Liu, 1994; Hu and Li, 1995; Liu *et al*., 1998; Wang *et al*., 1998; Cai *et al*., 1999; Yang *et al*., 2006a) (Table 3).

Unfortunately, the standards of evidence-based principles are sporadically applied in published clinical studies in this area. Published trials of medicinal herbs concerning endometriosis in the Chinese scientific journals of complementary medicine have generally not been conducted according to the guidelines of evidence-based medicine in Western scientific journals. One of the major difficulties in studying the clinical effects of herbal combinations in respect to evidence-based standards is that the composition of herbal formulae is individualized for each patient according to the different syndromes of endometriosis ('blood stasis syndrome'). Only one randomized controlled trial on the potential effects of medicinal herbs in endometriosis was identified after a thorough search in the English literature (Table 3) (Yang *et al*., 2006a). This study demonstrated that YWN (consisting of Chinese angelica, corydalis, curcuma, persica, red peony, safflower, salvia root and tortoise shell) was safe and its efficacy was similar to gestrinone in the prevention of post-operative recurrences of endometriosis. Other trials have been published only as

Table 1: Medicinal herbs and natural compounds used in the treatment of endometriosis and their biochemical constituents

English name	Chinese name	Main constituents
Bupleurum	Chai Hu	Triterpenoids (saikosaponin A–E, saikogenin F), essential oils, coumarin, flavone, carbohydrates
Chinese angelica	Dang Gui	Essential oils (ligustilide, n-butylphtalide), ferulic acid, scopletin
Cattail pollen (Typha)	Pu Huang	Isorhamnetin, pentacosane, alpha-sitosterol, arachidonic acid, palmitic acid, quercetin, sporopellin
Cinnamon twigs	Gui zhi	Essential oils (cinnamic-aldehyde, cinnamic acid, cinneylanine); coumarin
Cnidium fruit	Chuang Xiong	Alkaloids (tetramethylpyrazine); organic acids (ferulic acid, folic acid linoleic acid); essential oils; ligustilide
Corydalis	Yan Hu Suo	D-corydaline, corydalis L, dl-tetrahydropal-matine, coptisine, columbamine
Curcuma zeodaria	Yu Jin	Essential oils, curcumin, d-camphene, demethoxy-curcumin, turmerone, starch, lipids, carvone
Cyperus	Xiang Fu	Cyperene, cyperol, cyperol, isocyperol, cymene, limonene, camphene, cyperol, alpha-rotunol
Dahurian angelica	Bai Zhi	Coumarins; byakangelicol, cnidilin, scopoletin, phelopterin, xanthotoxin; essential oil
Frankincense	Ru Xiang	Triterpene acids, alpha-boswellic acids, beta-boswellic acids, basorin, alpha-phelandrene, pinene, arabic acid
Licorice root	Gan Cao	Triterpenoids (glycyrrhizin, glycyrrhetic acid), flavonoids (liguritine, liquiritigenin, uralene)
Myrrh	Mo Yao	Terpenoids; heerabomyrrholic acid, commiphoric acid, cinnamic aldehyde, resin, cumin aldehyde
Persica	Tao Ren	Essential oils (gibberellin A5); emulsin, allantoinase, lipids, vitamin B1
Poria	Fu Ling	Pachymose; pachyman, pachymaran, poriacic acid A, B and C, tumulosic acid
Red peony root	Chi Shao	Paeoniflorin, oxypaeoniflorin, lactiflorin, benzoylpaeonifloriin, daucosterol, d-catechin
Rhubarb	Da Huang	Sennoside (A–F), emodine, rhein, physcion, physcion monoglucoside, emodin monoglucoside
Salvia root	Dan Shen	Tanshinone (I, II_A, II_B,), militirone, tanshinol A, B, C, salviol, vitamin E
Scutellaria	Huang Qin	Baicalin, beicalein, wogonin, wogonoside, chrysin, tenaxin II, oroxylin A, skullcapflavone I, II
Sparganium	San Leng	Essential oils, starch
Tortoise shell[a]	Bie Jia	Gelatin, collagen, colloid, vitamin D, keratin
Tumeric	Jiang Huang	Curcumin, demethoxycurcumin, turmerone, arturmerone, curcuminoids, phellandrene, zingiberene
White Peony root	Bai Shao	Paeoniflorin, lactiflorin, paeonin, oxypaeoniflorin, hydroxypaeoniflorin, daucosterol

[a]Turtle/tortoise products have difficulty passing US customs with valid Cites certificates. We are not endorsing the use of animal-derived medicinals.

personal communications or as clinical observations in the English literature. At present, a randomized controlled trial is in progress in the USA evaluating the use of traditional Chinese medicine (TCM) at the Women's Health Research Unit of the Oregon Health Sciences University and the Oregon College of Oriental Medicine. The protocol (NCT00034047) is funded by the National Center for CAM (NCCAM). The study tests the hypothesis that TCM (acupuncture and medicinal herbs) will reduce endometriosis-related pelvic pain as effectively as nafarelin therapy without causing the pseudo-menopausal side effects that accompany GnRH-a therapy. Women were randomly assigned to receive either 12 weekly treatments of TCM or 12 weeks of the FDA-approved GnRH-a treatment. This will likely prove to be a landmark study in alternative endometriosis therapy.

Despite promising knowledge supporting the potential efficacy of herbal treatments in endometriosis and reports on the efficacy of medicinal herbs in related conditions (e.g. over 80% of pain relief, Table 3), the clinical effects of medicinal herbs on endometriosis remain unclear. Nevertheless, postulated experimental mechanisms of medicinal herbs include demonstrated cytokine suppression, COX-2 inhibition and antioxidant and antinociceptive activities. Treatment of endometriosis-associated symptoms with non-hormonal regimens is a particularly interesting treatment option for adolescent women with endometriosis. Hormonal anti-endometriosis therapies such as GnRH-a, progestins and oral contraceptives bear potential serious side effects, which limit their use in adolescents. As the efficacy of NSAIDs in women with endometriosis remains unclear, non-hormonal treatment of symptoms with medicinal herbs or herbal components may represent an innovative alternative for adolescents with endometriosis. Moreover, since herbal medicines may exert synergistic effects, these combinations may carry potential benefits of higher efficacy while minimizing toxicity.

Toxicity and herb–drug interactions

There is a potential for toxicity and untoward herb–drug interactions using medicinal herbs in the treatment of endometriosis (Table 4). Evidence on toxicity and herb–drug interactions of medicinal herbs used in the treatment of endometriosis is limited (Hoskins, 1984; Moing *et al*., 1987; Perry *et al*., 1990; Takasuna *et al*., 1995; Kuboniwa *et al*., 1999; Page and Lawrence, 1999; Ishihara *et al*., 2000; Li *et al*., 2001; Amato *et al*., 2002; Chainani-Wu, 2003; Elinav and Chajek-Shaul, 2003; Ikegami *et al*., 2003; Joshi *et al*., 2003; Wong and Chan, 2003; Chen and Chen, 2004; Wojcikowski *et al*., 2004a,b; Zhou *et al*., 2004; de Boer *et al*., 2005; Hu *et al*., 2005; Kelly *et al*., 2005; Ammon, 2006; Lao *et al*., 2006; Xie *et al*., 2006) (Table 4). Toxicity and untoward herb–drug interactions depend on factors associated with drugs (dose, dose regimen and therapeutic range) and as well as the consumer (age, genetic polymorphism, gender and pathological conditions). Toxicity and herb–drug interactions are unlikely to be evaluated because of the lack of current federal regulations in some industrialized countries, including the USA, and the paucity of research funding in this area. Established monitoring of adverse events caused by herb–drug

Table 2: Medicinal herbs and natural compounds used in the treatment of endometriosis and their anti-inflammatory effects

Herbs	Antiproliferative	Antinociceptive, sedative	Anti-inflammatory action			
			Antioxidant	Suppression		
				COX-2	Cytokines	NF-KappaB
Bupleurum	+				+	+
Chinese angelica	+	+	+		+	
Dahurian angelica root	+	+		+	+	+
Cattail pollen					+	
Cinnamon twigs		+		+		
Cnidium fruit	+	+				
Corydalis		+			+	
Curcuma (Turmeric)	+	+	+	+	+	+
Cyperus	+		+			
Frankincense	+	+			+	+
Licorice root	+	+		+	+	+
Myrrh		+	+		+	
Persica					+	
Poria	+	+		+	+	
Red peony root			+			
Rhubarb	+	+			+	+
Salvia root		+	+			+
Scutellaria	+			+	+	
Sparganium		+			+	
Tortoise shell[a]						+
White peony root				+	+	

[a]Turtle/tortoise products have difficulty passing US customs with valid Cites certificates.

interactions and increased financial support for studies investigating herb–drug interference would provide crucial information regarding public safety.

Effects of medicinal herbs, their active components and herbal combinations on cytokine expression

Suppression of the NF-Kappa B pathway and pro-inflammatory cytokines has been recognized as a major mechanism of conventional drug treatments for endometriosis; progestogens, GnRH-a, danazol and NSAIDs are known to demonstrate cytokine-suppressive activity (Boucher *et al*., 2000; Zhao *et al*., 2002; Wieser *et al*., 2005c; Yang *et al*., 2006b). Cytokines and chemokines such as tumour necrosis factor (TNF)-alpha, interleukin (IL)-1, IL-6, IL-8, monocyte chemotactic protein (MCP)-1 and regulated on activation, normal T cell expressed and secreted (RANTES) contribute to the pathogenesis of endometriosis by enhancing attachment, angiogenesis and/or proliferation of ectopic endometrial tissues in the pelvis (Bergqvist *et al*., 2001; Lebovic *et al*., 2001; Maas *et al*., 2001).

Curcuma zeodaria is used in many anti-endometriosis formulae (Shao, 1980; Cai, 1982; Lin *et al*., 1988; Jin, 1991; Qu, 1992; Hu and Li, 1995; Cai *et al*., 1999; Liu *et al*., 2006; Yang *et al*., 2006a). Curcuma zeodaria belongs to the plant family Zingiberaceae, which consists of ~80 different Curcuma species such as Curcuma longa (turmeric). Curcumin is a major active component of Curcuma. There are substantial *in vitro* and animal data indicating that curcumin has anti-inflammatory activity (Kumar *et al*., 1998; Siddiqui *et al*., 2006). Curcumin was shown to suppress the NF-KappaB pathway and NF-KappaB target cytokine genes (Takada *et al*., 2004) (Tables 1, 2, 5). Cao *et al*. demostrated anti-inflammatory effects of curcumin in endometrial stromal cells; curcumin inhibited NF-Kappa B induction of a pro-inflammatory and angiogenic cytokine, the macrophage migration inhibitory factor (MIF) in this endometriosis *in vitro* model (Cao *et al*., 2005). Recent studies could corroborate that curcumin arbitrates the effects by modulation of several important molecular targets, including NF-KappaB mediated gene expression (e.g. TNF, IL-1, IL-6), other transcription factors (e.g. AP-1, Egr-1, beta-catenin and PPAR-gamma), enzymes (e.g. COX2, iNOS), receptors (e.g. EGFR and HER2) and cell cycle proteins (e.g. cyclin D1 and p21) (Shishodia *et al*., 2005). Substantial research has shown for other anti-endometriosis herbs (e.g. Chinese angelica) that they modulate cytokine secretion, including TNF-alpha as demonstrated in a variety of model systems (Tseng and Chang, 1992; Lee *et al*., 1995; Jang *et al*., 2001; Van Dien *et al*., 2001; Xu *et al*., 2002; Tipton *et al*., 2003; Chen and Chen, 2004; Syrovets *et al*., 2005; Liu *et al*., 2006) (Table 5). Moreover, herbal combinations were shown to exert cytokine (e.g. TNF-alpha, IL-6, IL-8) suppressive effects studied in animal models of endometriosis (Yu *et al*., 2000; Qu *et al*., 2005). One example is YWN, a traditional anti-endometriosis formula (Table 3, 5), which decreased serum cytokine levels (e.g. TNF-alpha, IL-6 and IL-8) in a rodent model of endometriosis (Qu *et al*., 2005).

A sophisticated new approach to create novel, low-toxicity anti-inflammatory drugs is to design chemical analogues of naturally occurring medicinal herbal compounds. For example, newly developed synthetic analogues of curcumin (e.g. EF24-tripeptide

Table 3: Clinical studies on herbal combinations used in the treatment of endometriosis

Herbal combination	Formula name	Patients (*n*)	Efficacy[a]	Language	Authors
Chinese angelica, corydalis, curcuma, persica, red peony, safflower, salvia root, tortoise shell	YWN versus gestrinone versus untreated	20 versus 19 versus 13	NS[b]	English	Yang *et al.* (2006a)
Zeodaria, salvia root versus danazol	Dan'e recipe versus danazol	189 versus 160	NS[b]	Chinese	Cai *et al.* (1999)
Curcuma, cuscuta, epimedium, eupolyphaga, leech, parganium, pangolin versus danazol	Neiyixiao Recipe versus danazol	58 versus 45	NS[b]	Chinese	Liu *et al.* (1998)
Persica, rhubarb, succinum, tortoise shell	Neiyi Recipe #2	48	<0.05	Chinese	Wang *et al.* (1998)
Curcuma, eupolyphaga, leech, liquidambar, pangolin, prunella, sappan, scales, sparganium		48	97.6	Chinese	Hu *et al.* (1995)
Cinnamon, poria		46	91.3%	Chinese	Liu *et al.* (1994)
Corydalis, curcuma, cyperus, loranthus, salvia, sparganium, trogpterus		54	94%	Chinese	Qu *et al.* (1992)
Rhubarb, succinum, tortoise shell	Neiyi Recipe #1	76	89%	Chinese	Wang *et al.* (1991)
Complex formula[c]		74	96%	Chinese	Li *et al.* (1991)
Complex formula[d]	–	45	84%	Chinese	Jin *et al.* (1990)
Calamus, Chinese angelica, gum, san-chi, trogpterus, typha	Shixiao Guijie Tang	30	93%	Chinese	Zhuang *et al.* (1990)
Complex formula[e]	Shofu Zhuyu Tang	40	97.5%	Chinese	Lin *et al.* (1988)
Complex formula[f]	Xiao Yan San	60	78%	Chinese	Liu *et al.* (1983)
Complex formulae[g]	I Xuefu Zhuyu Tang II Shaofu Zhuyu Tang III Taoren Chengqi Tang			English	Cao *et al.* (1983)
Complex formula[h]		43	88%	Chinese	Cai *et al.* (1982)
Complex formula[i]		30	80%	Chinese	Dai *et al.* (1982)
Complex formulae[j]		156	82%	Chinese	Shao (1980)

[a]Efficacy rate (%) in terms of relief of dysmenorrhoeic symptoms.
[b]NS, No significant difference between herbal combination and danazol.
[c]Cattail pollen, cinnamon, curculigo, dioscorea, epimedium, frankincense, ligustrum, lyceum, mielettia, myrrh, root bark, rehmannia and salvia aconite.
[d]Angelica, artemisa anomala, asarum, cattail pollen, cinnamon twig, corydalis, Curcuma, gleditisa spine, hoelen, melia, moutan, persica, prunella, rubia, red peony, salvia, sparganium, tropterus, myrrh and san-chi.
[e]Shaofu Zhuyu Tang: bulrush, Chinese angelica, cinnamon bark, cnidium, corydalis, fennel, dry ginger, myrrh, red peony and trogopterus.
[f]Xiao Yao San: achyranthes, artemisia, astralgus, bupleurum, Chinese angelica; cinnamon bark, cnidium, Curcuma, carbonized cyperus, frankincencse, limestone, lindera, myrrh, phellodendron, carbonized rhubarb, salvia, sanqui, sparganium, trogpterus and typha.
[g]I: achyranthes bupleurum, carthamus, chih-ko, Chinese angelica, cnidium, licorice, persica, platycodon, raw rehmannia and red peony (additions: cattail pollen, Curcuma, sparganium, trogpterus); II: shaofu Zhuyu Tang: bulrush, Chinese angelica, cinnamon bark, cnidium, corydalis, dried ginger, fennel, myrrh, red peony, and trogopterus; III: taoren Chengqi Tang: achyranthes, Artemisia anomala, corydalis, moutan, persica, rhubarb, red peony, salvia.
[h]Chinese angelica, cinnamon, Curcuma, cyathula, cyperus, gleditisia spine, lacca, pangolin scales, salvia, sargassium, sparganium.
[i]Agrimony, bupleurum, cattail pollen, corydalis, cyperus, melia, moutan, patrinia, prunella, oyster shell, red peony, raw rehmania, salvia, saussurea, trogopterus.
[j]Group 1: bupleurum, bulrush, Chinese angelica, Curcuma, cyperus, gleditisia spine, pteropus, and sparganium, plus: centipede, earthworm, leech, tabanus; Group 2: salvia extract; Group 3: astralgus, bupleurum, cimicifuga bulrush, codonopsis, Curcuma, gleditisia spine, pteropus and sparganium; plus centipede, earthworm, leech, tabanus.

chloromethyl ketone) have been introduced to treat cancer and chronic inflammatory diseases (Selvam *et al.*, 2005; Ohori *et al.*, 2006; Sun *et al.*, 2006). This alternative approach to target key cytokines may establish drugs that lack the deleterious side effects of conventional, as well as potential, endometriosis drugs such as anti-TNF biologicals. Anti-TNF protein therapeutics were shown to have potentially severe side effects such as serious infection and to induce drug resistance in treated patients (Kenter and Cohen, 2006; Scott and Kingsley, 2006). Medicinal herbs or designed synthetic analogues of components of herbs with

Table 4: Toxicity and interactions of medicinal herbs used in the treatment of endometriosis (and typical clinical doses)

Herbs	Toxicity, Side effects	Interactions	LD_{50}	Authors
Bupleurum 3–10 g	Low toxicity; abdominal distention, constipation, edema	Tolbutamide, interferon	1.19 g/kg in mice (i.p.)	Xie *et al*. (2006); Chen and Chen (2004); Ikegami *et al*. (2003)
Chinese angelica 5–15 g	Low toxicity; hypotension; bleeding; Stimulated MCF-7 cells	Warfarin	100 g/kg in mice	Hu *et al*. (2005); Amato *et al*. (2002); Page and Lawrence (1999); Huang (1998)
Cattail pollen (Typha) 3–10 g	Well-tolerated; very low toxicity; nausea, allergy vomiting, constipation		35.57 g/kg in mice (i.p.)	Chen and Chen (2004); Huang (1998)
Cinnamon twigs 1–2 g	Low toxicity		18.48 ± 1.8 g/kg in mice (i.v.)	Chen and Chen (2004); Perry *et al*. (1990); Hoskins (1984)
Cnidium fruit 3–9 g	Lox toxicity	Anticoagulants	65.86 g/kg (i.p.)	Li *et al*. (2001)
Corydalis 3–10 g	Decreases heart rate, lowers blood pressure; CNS depression	Barbiturates	100 ± 4.53 g/kg in mice	Chen and Chen (2004); Huang (1998)
Curcuma zedoaria 6–12 g	Relatively safe; nausea, vomiting, burning sensation, fatigue	Anticoagulants	16.75 g/kg in mice	Chen and Chen (2004); Huang (1998)
Cyperus 6–12 g	Malaise, sore throat, headache		1500 mg for cyperone in mice (i.p.)	Chen and Chen (2004)
Dahurian angelica 3–10 g	Increase of blood pressure; seizures, convulsions	Tolbutamide, diazepam, testosterone	53.82 g/kg in mice	Hu *et al*. (2005); Chen and Chen (2004); Ishihara *et al*. (2000)
Frankincense 3–10 g	Nausea, vomiting, epigastric pain			Ammon (2006); Chen and Chen (2004)
Licorice root 3–10 g	Hypertension, sodium retention, headache, hypokalemia	Digoxin, Cortircosteroids	6.84 g/kg in mice (i.p.)	Zhou *et al*. (2004); Chen and Chen (2004); Elinav and Chajek-Shaul (2003)
Myrrh 3–10 g	Nausea vomiting			Chen and Chen (2004)
Persica 6–10 g	Cyanide poisoning	Anticoagulants	222 g/kg in mice	Chen and Chen (2004); Moing *et al*. (1987)
Poria 10–15 g	No significant side effects; diuretic	Diuretics	500 times the adult normal dose increased leucocytes (dogs)	Chen and Chen (2004)
Red peony root 6–15 g	Well-tolerated	Anticoagulants (warfarin)	Maximum safe dose is 50 g/kg in mice (i.v.)	Chen and Chen (2004); Wong and Chan (2003)
Rhubarb 5–10 g	Nausea, vomiting, poor appetite, diarrhea;	Cardiac glycosides	153 g/kg in mice (oral)	Chen and Chen (2004); Wojcikowski *et al*. (2004b)
Salvia root 5–10 g	Relatively non-toxic	Anticoagulants, digoxin	80.5 ± 3.1 g/kg in mice	Hu *et al*. (2005); Chen and Chen (2004); Huang (1998)
Scutellaria 3–10 g	Hepatoprotective; diarrhea	Irrinotecan, beta-lactam antibiotics	3081 mg/kg of baicalein in mice (i.p.)	Hu *et al*. (2005); de Boer *et al*. (2005); Chen and Chen (2004); Takasuna *et al*. (1995)
Sparganium 3–10 g		Anticoagulants	233.9 ± 9.9 g/kg in mice (oral)	Chen and Chen (2004)
Tortoise shell 10–30 g	Allergy			Chen and Chen (2004)
Turmeric 3–10 g	Relatively safe, minimal toxicity; nausea, vomiting	Anticoagulants	50 times the adult dose for 30 days was not toxic in rats	Lao *et al*. (2006); Joshi *et al*. (2003); Chainani-Wu (2003)
White Peony root 5–10 g	Drowsiness, sedation	Anticoagulants, sedatives; antidiabetics	9.53 mg/kg in mice (i.p.)	Chen and Chen (2004)

cytokine-modulating effects may provide low-toxicity alternatives to treat endometriosis-associated symptoms (Adams *et al*., 2004).

Effects of medicinal herbs, their active components and herbal combinations on the prostanoid pathway

The prostanoid pathway is suggested to be one of the key targets involved in the pathogenesis of endometriosis. Locally produced PGE_2, a potent stimulator of aromatase, upregulates estrogen production, which in turn stimulates COX-2 to increase PGE_2 leading to increased endometrial cell proliferation in endometriosis (Noble *et al*., 1997; Attar and Bulun, 2006). COX-2-selective inhibitors were shown to exert anti-proliferative effects (Hasegawa *et al*., 2005), to decrease implant size in rodent models of endometriosis (Dogan *et al*., 2004; Matsuzaki *et al*., 2004) and to diminish endometriosis associated-pain in a clinical setting (Cobellis *et al*.,

Table 5: Cytokine suppressive effects of medicinal herbs and herbal formulae used in endometriosis

Herb/Combination	Major active component	Cytokines inhibited	Model	Author
White peony root	Paeoniflorin	TNF-alpha, IL-6	*In vitro*	Liu *et al.* (2006)
Frankincense	Boswellic acids	TNF-alpha	*In vitro*	Syrovets *et al.* (2005)
Myrrh		IL-6, IL-8	*In vitro*	Tipton *et al.* (2003)
Scutellaria	Wogonin	TNF-alpha	*In vitro*	Van Dien *et al.* (2001)
Curcuma	Curcumin	TNF-alpha	*In vitro*	Jang *et al.* (2001)
Poria		TNF-alpha, IL-1, IL-6	*In vitro*	Tseng *et al.* (1992)
YWN[a]	Formula	TNF-alpha, IL-6, IL-8	Murine	Qu *et al.* (2005)
Scutellaria	Wogonin	TNF-alpha	Murine	Van Dien *et al.* (2001)
Sparganium		IL-8	Murine	Lee *et al.* (1995)
Chinese angelica	Essential oils	TNF-alpha	Rabbit	Xu *et al.* (2002)

[a]*Chinese angelica*, corydalis, curcuma, persica, red peony, safflower, salvia root and tortoise shell.

2004). Among medicinal anti-endometriosis herbs that inhibit the prostanoid system, dahurian angelica root, cinnamon, licorice root, poria, scutellaria, Curcuma and the formulae KBG, YWN and Neiyi have been best studied (Wang *et al.*, 1991; Mori *et al.*, 1993; Yu *et al.*, 1993; Wang *et al.*, 1998; Giner-Larza *et al.*, 2000; Park *et al.*, 2001; Hong *et al.*, 2002; Huss *et al.*, 2002; Ban *et al.*, 2003; Prieto *et al.*, 2003; Furuhashi *et al.*, 2005; Qu *et al.*, 2006) (Table 6). Cinnamon and poria, both exhibiting COX-2 suppressive activity, are components of the anti-endometriosis herbal formula KBG (consisting of five different herbs cinnamon, poria, red peony, persica and tree peony bark). Treatment with the KBG formula suppressed spontaneous development of adenomyosis in a murine endometriosis model (Mori *et al.*, 1993). The beneficial effects of KBG in the murine endometriosis model may be attributed to the COX-2 inhibiting effect of KBG's constituents poria and cinnamon. YWN, an herbal composition (Chinese angelica, corydalis, curcuma, persica, red peony, safflower, salvia root, tortoise shell) (Table 6), reduced expression of COX-2 mRNA in endometriotic tissues in a rat model (Qu *et al.*, 2006). Furthermore, the anti-endometriosis herbal recipe Neiyi (Table 6) decreased prostaglandins (e.g. PGE_2, PgF_1-alpha) levels in clinical settings in women with endometriosis (Wang *et al.*, 1991; Wang *et al.*, 1998; Wu *et al.*, 2000).

The highly regulated enzyme COX-2, which catalyzes prostaglandin production, has become a popular target for the development of new anti-inflammatory drugs. However, some of the COX-2 selective NSAIDs possess gastrointestinal side effects. In addition, recent data suggest that chronic use of COX-2 inhibitors is associated with increased cardiovascular risk (Vonkeman *et al.*, 2006). As a consequence, some of the COX-2 selective NSAIDS were labelled with black box warning or withdrawn from the market. In the light of recent reports of serious unintended effects and black box warnings of COX-2 selective drugs, plants with direct or indirect suppressive effects on prostanoids (Huss *et al.*, 2002) represent a potential alternative resource of COX-2 selective inhibitors.

Effects of medicinal herbs, their active components and herbal combinations on oxidative status

Reactive oxygen species (ROS) are suggested to play a role in the pathogenesis of endometriosis (Murphy *et al.*, 1998). Retrograde menstruation allows transport of pro-oxidant factors, such as heme, iron and apoptotic endometrial cells, which are well-known inducers of oxidative stress, into the peritoneal cavity of women with endometriosis (Van Langendonckt *et al.*, 2002). ROS can promote growth of endometrial stromal cells (Foyouzi *et al.*, 2004). Antioxidants, such as vitamin E, showed beneficial effects in an *in vitro* model of endometrial proliferation (Foyouzi *et al.*, 2004) and anti-inflammatory effects in a rodent model of LPS-induced inflammation leading to increased embryo viability (Mayorga *et al.*, 2004). Drugs with antioxidant properties, such as SPRMs, have been developed as possible treatment choices for endometriosis (Roberts *et al.*, 1996), but conclusive evidence on the benefits of the various modalities is lacking.

Commonly used 'anti-endometriosis' herbs such as Chinese angelica, curcuma and salvia root, turmeric and herbal formulae (e.g. KBG) have potent anti-oxidant effects (Cao *et al.*, 1996; Yoshioka *et al.*, 1998; Quiles *et al.*, 2002; hou *et al.*, 2004; Kang *et al.*, 2004; Moussaieff *et al.*, 2005; Sekiya *et al.*, 2005;

Table 6: Suppressive effects on the prostanoid pathway of medicinal herbs and combinations used for endometriosis

Herb/Combination	Major active component	Suppression of prostanoids	Model	Author
Licorice	Licochalcone A	Phopholipase-2, COX-2, PGE2	*In vitro*	Furuhashi *et al.* (2005)
Dahurian angelica	Coumarin, furucocoumarin	COX-2, PGE2	*In vitro*	Ban *et al.* (2003)
Curcuma	Curcumin, Ceta- (or ar-) turmerone	PGE2	*In vitro*	Hong *et al.* (2002)
Cinnamon	Cinnamonaldehyde	COX-2	*In vitro*	Huss *et al.* (2002)
YWN[a]	Formula	COX-2	Murine	Qu *et al.* (2006)
Poria	Pachymic acids	Phospholipase-A2	Murine	Prieto *et al.* (2003)
Scutellaria	Wogonin	COX-2	Murine	Park *et al.* (2001)
Neiyi[b]	Formula	PGE2, PGF2-alpha	Human	Wang *et al.* (1998)

[a]*Chinese angelica*, corydalis, curcuma, persica, red peony, safflower, salvia root and tortoise shell.
[b]Persica, rhubarb, succinum and tortoise shell.

Zhou *et al*., 2005; El-Ashmawy *et al*., 2006) (Table 7). The ability of KBG and vitamin E to prevent atherosclerosis was compared in diet-induced hypercholesterolemic rabbits (Sekiya *et al*., 2005). KBG had a stronger anti-oxidant effect than vitamin E shown in this animal model. The superiority of the herbal combination KBG to vitamin E in this animal likely relates to synergistic interactions within the herbal combination.

In this context, it is noteworthy to mention that although increased serum levels of vitamin E levels were associated with decreased risk for cancer and cardiovascular diseases (Stahelin *et al*., 1991), exogenous oral administration of the antioxidant vitamin E did not show benefits in cancer and cardiovascular disease in human intervention studies (Brown *et al*., 2001; Lichtenstein and Russell, 2005). Data from the HOPE and HOPE-TOO trials showed that vitamin E did not decrease fatal or non-fatal cancer (Lonn *et al*., 2005). Vitamin E alone also did not reduce myocardial infarction, stroke, CVD death and other cardiovascular morbidities; instead vitamin E increased hospitalization for heart failure (Lonn *et al*., 2005). In contrast to these findings, diets high in vitamin E showed beneficial influence on the incidence on cardiovascular health and cancer risk (Knoops *et al*., 2004; Lichtenstein and Russell, 2005). In an elderly population (70–90 years), adherence to a Mediterranean diet and healthful lifestyle is associated with a more than 50% lower rate of all-causes and cause-specific mortality (HALE project) (Knoops *et al*., 2004). In combination, these studies (HOPE and HALE projects) suggest that either vitamin E has limited or no benefit or that it has benefit only in combination with other food-related substances. In an Italian endometriosis population, higher intake of green vegetables and fresh fruit caused a significant reduction of the risk for endometriosis (Parazini *et al.*, 2004). Interpretation of nutritional studies on the effect of dietary patterns on cancer and cardiovascular disease prevention led to the definition of the 'whole food' concept (Temple and Galdwin, 2003). Several components in fruits and vegetables with beneficial effects are postulated to prevent disease via their synergistic effects. This 'teamwork' principle is likely to hold for synergistic herbal therapies as well, but research will be needed to delineate optimal combinations.

Anti-nociceptive of medicinal herbs, their active components and herbal combinations used in the treatment of endometriosis

The cellular and neural mechanisms of pelvic pain associated with endometriosis are poorly understood (Gambone *et al*., 2002). It has been proposed that direct invasion of pelvic nerves by endometriotic implants or nearby release of inflammatory humoral factors (e.g. prostaglandins, cytokines) stimulate sensory and parasympathetic afferents that carry the perceived painful stimuli (Tulandi *et al*., 1998). Ectopic endometrial growths themselves develop autonomic and sensory innervations (Berkley *et al*., 2005).

Drugs most commonly prescribed to treat endometriosis pain symptoms, particularly dysmenorrhea, are NSAIDs, combined oral contraceptives (COC), and other analgesics (e.g. paracetamol). Evidence of the efficacy of COC on dysmenorrhea remains to be determined (Proctor *et al*., 2001), and there has been reluctance to use the COC at young ages because of possible long-term health risks. The evidence on the efficacy of NSAIDs in the treatment of endometriosis is inconclusive (Allen *et al*., 2005). Moreover, therapy with NSAIDs can bear side effects. Women using NSAIDs and even over the counter painkillers such as acetaminophen need to be aware of the possibility that these drugs may cause serious unintended effects including increased risk of cardiovascular events, hypertension and gastric ulceration (Dedier *et al*., 2002; Forman *et al*., 2005; Johnsen *et al*., 2005).

Since ancient times, herbal medicine has been used to relieve pain and discomfort from wounds and burns. Evidence confirms pain alleviating mechanisms of several medicinal herbs used for endometriosis (e.g. cnidium fruit, corydalis, curcuma, dahurian angelica, frankincense, myrrh and white peony root) and herbal formulae (e.g. Neiyi) (Tuttle *et al*., 1989; Liu *et al*., 1990; Yu *et al*., 1993; Yu *et al*., 1995; Dolara *et al*., 1996; Wang *et al*., 1998; Wei *et al*., 1999; Zhang *et al*., 2000; Tsai *et al*., 2001; Navarro Dde *et al*., 2002; Kimmatkar *et al*., 2003; Tatsumi *et al*., 2004; Yuan *et al*., 2004; Zhou *et al*., 2005) (Table 8).

Corydalis is one of the most commonly used herbs in pain related syndromes (Chen and Chen, 2004), and is also used in many Chinese formulae designed for the treatment of endometriosis-associated pain (Dai, 1982; Cao, 1983; Lin *et al*., 1988; Jin, 1991; Qu, 1992; Wieser *et al*., 2005a,b; Yang *et al*., 2006a) (Table 3). Tetrahydropalmatine (THP) is thought to be the main active pharmacological component of cordyalis (Brown *et al*., 2001); THP has been shown to exhibit anti-inflammatory, sedative, analgesic, hypnotic and muscle relaxant properties shown *in vitro* and rodent models (Wei *et al*., 1999; Chen and Chen, 2004).

Anti-nociceptive CAM treatments are gaining increased popularity for treatment of dysmenorrhoea in industrialized countries (Fugh-Berman and Kronenberg, 2003). Therapies shown to be potentially effective in the treatment of dysmenorrhoea include vitamin E (Butler and McKnight, 1955), vitamin B1 (Gokhale, 1996; Wilson and Murphy, 2001) and ω-3 fatty acids (fish oil) (Deutch, 1995). One randomized controlled trial was conducted

Table 7: Antioxidant effects of medicinal herbs and herbal combinations used in endometriosis

Herb	Major active component	Antioxidant effect	Model	Author
Chinese angelica	Essential oils	Increased of SOD[a] and catalase	*In vitro*	Hou *et al*. (2004)
Salvia root		Reduced ROS	*In vitro*	Kang *et al*. (2004)
Salvia root	Tanshinone II-A Lithospermic acid B	Reduced ROS	*In vitro*	Cao *et al*. (1996)
Myrrh		Increased glutathione S-transferase	Murine	El-Ashmawy *et al*. (2006)
KBG[b]	Formula	Reduced lipid peroxide levels	Rabbit	Sekiya *et al*. (2005)
Turmeric	Curcumin	Increased antioxidants	Rabbit	Quiles *et al*. (2002)

[a]SOD, superoxide dismutase.
[b]Cinnamon, poria, red peony, persica, tree peony bark.

Table 8: Anti-nociceptive effects of medicinal herbs and combinations used in endometriosis

Herb	Major active component	Postulated mechanisms	Model	Author
Curcuma	Curcumenol		Murine	Navarro *et al*. (2002)
White peony root	Paeoniflorin	Opioid receptor (kappa)	Murine	Tsai *et al*. (2001)
Corydalis	Tetrahydropalamatine	Opioid, dopaminergic, and GABAergic mechanisms	Murine	Wei *et al*. (1999)
Myrrh	Furanoeudesma-1,3-diene	Opioid mechanisms	Murine	Dolara *et al*. (1996)
Cnidium fruit	Tetramethylpyrazine	Blocked uterine responsiveness to PGE2	Murine	Tuttle *et al*. (1989)
Salvia root		CNS	Cat	Liu *et al*. (1990)
Corydalis	Tetrahydropalamatine	Opioid, dopaminergic, and GABAergic mechanisms	Human	Yuan *et al*. (2004)
Dahurian angelica		Opioid, dopaminergic, and GABAergic mechanisms	Human	Yuan *et al*. (2004)
Frankincense	Boswellia serrata		Human	Kimmatkar *et al*. (2003)
Neiyi[a]	Formula	Increased beta-endorphin levels	Human	Yu *et al*. (1995)
Neiyi[a]	Formula	Increased beta-endrophin levels	Human	Yu *et al*. (1993)

[a]Rhubarb, persica, succinum, tortoise shell (formulae are modified according syndromes).

to evaluate the efficacy of an herbal combination consisting of corydalis, Chinese angelica and white peony root on the efficacy of dysmenorrhoea (Kennedy *et al*., 2006); however, the sample size of this trial was too small. Herbal therapy may serve as a potential alternative especially for young adults with endometriosis-associated pain syndromes.

Discussion

A significant increase in lifetime use of herbs and other natural products was noted from 12.1% to 18.6% between 1998 and 2002 in the USA (Tindle *et al*., 2005). On 16 May 2002, the WHO released its first global strategy on traditional medicines and announced that it will be greatly extending its activities in non-allopathic therapies. Several important drugs are derived from natural products: aspirin (1889; from willow bark), penicillin (1940s; from fungus), artemisinin (1980; from quinghaosu), mevacor (1987; from fungus), taxol (1993; from the pacific yew tree) and byetta (2005; from Gila monster saliva). It is hoped that medicinal herbs or combinations of medicinal herbs and drugs will promote health and well being, while minimizing toxicities and side effects.

Alternative pain therapies have gained popularity particularly among women with endometriosis. It is predicted that CAM will be used in combination with allopathic medicine or will completely replace standard pharmacological options for some women with endometriosis as shown in an Australian population (Cox *et al*., 2003). Despite the lack of rigorous evidence, many recipients of herbal therapy view these natural products to be safer and more effective alternatives to Western medicine. Other CAM users believe them to be more compatible with their beliefs even if they are less efficacious than conventional therapy (Astin *et al*., 2000). In view of the need for alternatives in pain management, CAM therapies such as medicinal herbs and other botanicals with anti-inflammatory and pain-alleviating properties may be useful particularly in the treatment of endometriosis-associated symptoms. Herbal medicine has been prescribed safely by professionals in the USA for many years; however, there are only few formal studies on safety and efficacy of combining herbal combinations with prescription drugs.

Although clinical studies on herbs in the literature show promising effects, conclusive clinical evidence of the efficacy of medicinal herbs in the treatment of endometriosis-associated pain is lacking. The effects of Chinese herbal medicine for treating endometriosis remain unclear for several reasons. First, most herbs currently used in human populations have been available for the last 2000 years and no efficient regulation mechanisms control their use (Wolsko *et al*., 2005). Since 1994, phytomedicinal products (medicines derived from plants) are legally classified in the USA as dietary supplements. Included in this category are vitamins, minerals, herbs or other botanicals, amino acids and other dietary substances derived from animals or plants. The US Food and Drug Administration lacks quality standards (De Smet, 2005) and does not require levels of therapeutic evidence in the form of randomized clinical trials before such products are marketed to consumers. Some European countries, such as Germany and France, were among the first to introduce simplified registration procedures for herbal products. In order to harmonize different registration procedures, the European parliament has installed specific regulatory mechanisms covering medicinal herbal products (De Smet, 2005). Directive 2004/24/EC requires a special, but simplified registration procedure for certain medicinal products (De Smet, 2005). In addition, European legislation introduced a list of recognized herbs and mandates adverse-event reporting. Secondly, specific mechanisms of action of herbs are underreported and have not been tested using appropriate study designs including *in vitro* and animal models (Cao *et al*., 2005; Qu *et al*., 2005; Wieser *et al*., 2005b). Finally, single herbs (e.g. Curcuma) and herbal combinations are composed of a number of bioactive compounds, complicating the investigation of their mechanisms of actions. Benefits of the inherent synergism within single herbs and herbal combinations are enhanced efficacy and reduced toxicity. Of course, liabilities are also possible as some interacting substances might compete with each other or increase toxicity. The potential for both positive and negative interactions necessitates careful study and validations of existing and new permutations.

Investigations of the efficacy, toxicity and herb–herb and drug–herb interactions should include testing in *in vitro* and rodent (e.g. rat) models and subhuman primate models (e.g. baboon) of endometriosis (Ryan *et al*., 1994; D'Hooghe, 1997; Awwad *et al*., 1999; Fazleabas *et al*., 2002). Moreover, investigators should be encouraged to provide information on the purity, quality and composition of the herbs tested in experimental trials. Standardization would enhance interpretation of CAM data and thus the applicability of the findings. After acquiring mechanistic and safety

data, we propose that randomized clinical trials be planned and implemented using human subjects with endometriosis. Adolescents with endometriosis are the most likely to benefit from disease prevention, preservation of fertility and pain relief with innovative herbal treatments. The use of standard 'single drug' hormonal endometriosis regimens (e.g. GnRH-a, danazol and progestagens) is most likely to have untoward side effects and long-term morbidities in this important patient population.

Conclusion

Over the next 20 years, major shifts are likely to occur in the use of herbal compounds, vitamins, minerals, supplements, nutraceuticals or whole food nutrition. We should anticipate a wave of new natural medicines based on scientifically substantiated health claims. In the near future, we predict that more US adults will use medicinal herbs and herbal products to treat their diseases as we change our perspective from treating disease to promoting better health. Formal clinical trials testing the mechanisms of action, efficacy and toxicities of CAM therapies are needed. The establishment of the NCCAM Institute of the NIH was an important step towards the validation of popular and effective traditional treatments (Stokstad, 2000). Despite the limited growth in the NIH, the Fiscal Year (FY) 2006 President's budget for the NCCAM increased to $122 692 000. NCCAM has sponsored several clinical trials on the efficacy of medicinal herbs in the treatment of irritable bowel syndrome, menopausal symptoms, hepatitis C, AIDS and cancer.

Controlled clinical studies will be needed to clarify the clinical efficacy of natural medicinal herbs or synthetic herbal analogues in the treatment of endometriosis-associated pain and investigate herb–herb and drug–herb interactions and other toxicities. A potential benefit of herbal therapy is the likelihood of synergistic interactions within individual (e.g. Curcuma) or combinations of plants and the constraint of untoward side effects. Experimental and epidemiological data (e.g. HOPE and HALE trials) infer that health promotion involves addressing many important determinants rather than adjusting the level of a single substance. We, therefore, believe that it is critical to establish streamlined registration procedures for natural medicinal products, particularly herbal ones that have a long tradition of safe use.

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