

A Comprehensive Review of Studies Related to Chinese Herbal Medicine and Traditional Chinese Medicine (TCM) in Conjunction with Assisted Reproductive Technology (ART), IVF, and IUI for Male and Female Infertility

by Ray Rubio, DAOM, L. Ac. (FABORM)

1. Hum Fertil (Camb). 2003 Nov;6(4):161-8.

Application of traditional Chinese medicine in the treatment of infertility.

Xu X, Yin H, Tang D, Zhang L, Gosden RG.

The Jones Institute for Reproductive Medicine, Department of Obstetrics and Gynaecology, Norfolk, VA 23507, USA.

Abstract

The philosophy and practice of traditional Chinese medicine (TCM) have been evolving for thousands of years in China, Japan and other Asian countries. TCM is now generating popular interest worldwide for reproductive health care and disease prevention, including applications for treating infertility and improving sexual function. This review focuses on the application of TCM for infertility patients, and provides a critical reflection on the efficacy and safety of selected Chinese herbal formulas. It has been claimed that some formulas produce high clinical pregnancy rates with few or no side effects, as well as improving the general well-being of patients. The need for randomized control trials and research into possible mechanisms of action, effective doses, contra-indications and toxicity is self-evident. However, the task is enormous in view of the number of herbal products currently available on the market; yet among these products are undoubtedly some that will prove to be safe and beneficial.

PMID: 14614194 [PubMed - indexed for MEDLINE]

2. Curr Opin Obstet Gynecol. 2008 Jun;20(3):211-5.

Traditional Chinese medicine and infertility.

Huang ST, Chen AP.

Department of Chinese Medicine, Chang Gung Memorial Hospital-Kaohsiung Medical Center, Chang Gung Institute of Technology, Taiwan, ROC.
shenteng@adm.cgmh.org.tw

Abstract

PURPOSE OF REVIEW: The present review gives an overview of the potential use of traditional Chinese medicine in the treatment of infertility, including an evidence-based evaluation of its efficacy and tolerance.

RECENT FINDINGS: Recent studies demonstrated that traditional Chinese medicine could regulate the gonadotropin-releasing hormone to induce ovulation and improve the uterus blood flow and menstrual changes of endometrium. In addition, it also has impacts on patients with infertility resulting from polycystic ovarian syndrome, anxiety, stress and immunological disorders. Although study design with adequate sample size and appropriate control for the use of traditional Chinese medicine is not sufficient, the effective studies have already indicated the necessity to explore the possible mechanisms, that is, effective dose, side effect and toxicity of traditional Chinese medicine, in the treatment of infertility by means of prospective randomized control trial.

SUMMARY: The growing popularity of traditional Chinese medicine used alone or in combination with Western medicine highlights the need to examine the pros and cons of both Western and traditional Chinese medicine approaches. Integrating the principle and knowledge from well characterized approaches and quality control of both traditional Chinese medicine and Western medical approaches should become a trend in existing clinical practice and serve as a better methodology for treating infertility.

PMID: 18460933 [PubMed - indexed for MEDLINE]

3. Chin J Integr Med. 2006 Dec;12(4):312-6.

Progress of integrative Chinese and Western medicine in treating polycystic ovarian syndrome caused infertility.

Song JJ, Yan ME, Wu XK, Hou LH.

Gynecological and Obstetric Department, First Hospital, Heilongjiang University of Traditional Chinese Medicine, Harbin (150040).

Abstract

Polycystic ovarian syndrome (PCOS) is one of the most popular diseases that cause menstrual dysfunction and infertility in women. The present paper is a brief retrospection on the progress in treatment of PCOS caused infertility with integrative Chinese and Western medicine (ICWM). It can be seen from these materials that using traditional Chinese medicine (TCM) recipes formulated by Shen-replenishing herbs or acupuncture to reinforce Gan-Shen, regulate Chong-Ren Channels in treating PCOS, stable clinical efficacy could be obtained, with less adverse reaction, though the effect initiated somewhat late. Whereas, when Shen-replenishing recipe and acupuncture are combined with hormone or ovulation promoting drugs of Western medicine, the above-mentioned shortcomings would be overcome. So, this combined therapy is frequently used in clinical practice.

PMID: 17361532 [PubMed - indexed for MEDLINE]

4. Cochrane Database Syst Rev. 2009 Jul 8;(3):CD006568.

Chinese herbal medicine for endometriosis.

Flower A, Liu JP, Chen S, Lewith G, Little P.

Complementary Medicine Research Unit , Dept Primary Medical Care, Southampton University, Norlington Gate Farmhouse, Norlington Lane, Ringmer, Sussex, UK, BN8 5SG.

Abstract

BACKGROUND: Endometriosis is characterized by the presence of tissue that is morphologically and biologically similar to normal endometrium in locations outside the uterus. Surgical and hormonal treatment of endometriosis have unpleasant side effects and high rates of relapse. In China, treatment of endometriosis using Chinese herbal medicine (CHM) is routine and considerable research into the role of CHM in alleviating pain, promoting fertility, and preventing relapse has taken place.

OBJECTIVES: To review the effectiveness and safety of CHM in alleviating endometriosis-related pain and infertility.

SEARCH STRATEGY: We searched the Menstrual Disorders and Subfertility Group Trials Register, Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library) and the following English language electronic databases (from their inception to the present): MEDLINE, EMBASE, AMED, CINAHL, NLH on the 30/04/09. We also searched Chinese language electronic databases: Chinese Biomedical Literature Database (CBM), China National Knowledge Infrastructure (CNKI), Chinese Sci & Tech Journals (VIP), Traditional Chinese Medical Literature Analysis and Retrieval System (TCMLARS), and Chinese Medical Current Contents (CMCC).

SELECTION CRITERIA: Randomised controlled trials (RCTs) involving CHM versus placebo, biomedical treatment, another CHM intervention, or CHM plus biomedical treatment versus biomedical treatment were selected. Only trials with confirmed randomisation procedures and laparoscopic diagnosis of endometriosis were included.

DATA COLLECTION AND ANALYSIS: Risk of bias assessment, and data extraction and analysis were performed independently by three review authors. Data were combined for meta-analysis using relative risk (RR) for dichotomous data. A fixed-effect statistical model was used, where appropriate. Data not suitable for meta-analysis are

presented as descriptive data.

MAIN RESULTS: Two Chinese RCTs involving 158 women were included in this review. Both these trials described adequate methodology. Neither trial compared CHM with placebo treatment. There was no evidence of a significant difference in rates of symptomatic relief between CHM and gestrinone administered subsequent to laparoscopic surgery (95.65% versus 93.87%; risk ratio (RR) 1.02, 95% confidence interval (CI) 0.93 to 1.12, one RCT). The intention-to-treat analysis also showed no significant difference between the groups (RR 1.04, 95% CI 0.91 to 1.18). There was no significant difference between the CHM and gestrinone groups with regard to the total pregnancy rate (69.6% versus 59.1%; RR 1.18, 95% CI 0.87 to 1.59, one RCT). CHM administered orally and then in conjunction with a herbal enema resulted in a greater proportion of women obtaining symptomatic relief than with danazol (RR 5.06, 95% CI 1.28 to 20.05; RR 5.63, 95% CI 1.47 to 21.54, respectively). Overall, 100% of women in all the groups showed some improvement in their symptoms. Oral plus enema administration of CHM showed a greater reduction in average dysmenorrhoea pain scores than did danazol (mean difference (MD) -2.90, 95% CI -4.55 to -1.25; $P < 0.01$). Combined oral and enema administration of CHM showed a greater improvement, measured as the disappearance or shrinkage of adnexal masses, than with danazol (RR 1.70, 95% CI 1.04 to 2.78). For lumbosacral pain, rectal discomfort, or vaginal nodules tenderness, there was no significant difference either between CHM and danazol.

AUTHORS' CONCLUSIONS: Post-surgical administration of CHM may have comparable benefits to gestrinone but with fewer side effects. Oral CHM may have a better overall treatment effect than danazol; it may be more effective in relieving dysmenorrhea and shrinking adnexal masses when used in conjunction with a CHM enema. However, more rigorous research is required to accurately assess the potential role of CHM in treating endometriosis.

PMID: 19588398 [PubMed - indexed for MEDLINE]

5. Cochrane Database Syst Rev. 2007 Oct 17;(4):CD005288.

Chinese herbal medicine for primary dysmenorrhoea.

Zhu X, Proctor M, Bensoussan A, Smith CA, Wu E.

Chinese Medicine Program, University of Western Sydney, Center for Complementary Medicine Research, Bldg 3, Bankstown Campus, Locked Bag 1797, Penrith South DC, Sydney, New South Wales, Australia, 2750. x.zhu@uws.edu.au

Update in: Cochrane Database Syst Rev. 2008;(2):CD005288.

Abstract

BACKGROUND: Conventional treatment for primary dysmenorrhoea (PD) has a failure rate of 20% to 25% and may be contraindicated or not tolerated by some women. Chinese herbal medicine (CHM) may be a suitable alternative.

OBJECTIVES: To determine the efficacy and safety of CHM for PD when compared with placebo, no treatment, and other treatment.

SEARCH STRATEGY: The Cochrane Menstrual Disorders and Subfertility Group Trials Register (to 2006), MEDLINE (1950 to January 2007), EMBASE (1980 to January 2007), CINAHL (1982 to January 2007), AMED (1985 to January 2007), CENTRAL (The Cochrane Library issue 4, 2006), China National Knowledge Infrastructure (CNKI, 1990 to January 2007), Traditional Chinese Medicine Database System (TCMDS, 1990 to Dec 2006), and the Chinese BioMedicine Database (CBM, 1990 to Dec 2006) were searched. Citation lists of included trials were also reviewed.

SELECTION CRITERIA: Any randomised controlled trials (RCTs) involving CHM versus placebo, no treatment, conventional therapy, heat compression, another type of CHM, acupuncture or massage. Exclusion criteria were identifiable pelvic pathology and dysmenorrhoea resulting from the use of an intra-uterine contraceptive device (IUD).

DATA COLLECTION AND ANALYSIS: Quality assessment, data extraction and data translation were performed independently by two review authors. Attempts were made to contact study authors for additional information and data. Data were combined for meta-analysis using either Peto odds ratios or relative risk (RR) for dichotomous data or weighted mean difference for continuous data. A fixed-effect statistical model was used, where suitable. If data were not suitable for meta-analysis, any available data from the trial were extracted and presented as descriptive data.

MAIN RESULTS: Thirty-nine RCTs involving a total of 3475 women were included in the review. A number of the trials were of small sample size and poor methodological quality. Results for CHM compared to placebo were unclear as data could not be combined (3 RCTs). CHM resulted in significant improvements in pain relief (14 RCTs; RR 1.99, 95% CI 1.52 to 2.60), overall symptoms (6 RCTs; RR 2.17, 95% CI 1.73 to 2.73) and use of additional medication (2 RCTs; RR 1.58, 95% CI 1.30 to 1.93) when compared to use of pharmaceutical drugs. Self-designed CHM resulted in significant

improvements in pain relief (18 RCTs; RR 2.06, 95% CI 1.80 to 2.36), overall symptoms (14 RCTs; RR 1.99, 95% CI 1.65 to 2.40) and use of additional medication (5 RCTs; RR 1.58, 95% CI 1.34 to 1.87) after up to three months follow up when compared to commonly used Chinese herbal health products. CHM also resulted in better pain relief than acupuncture (2 RCTs; RR 1.75, 95% CI 1.09 to 2.82) and heat compression (1 RCT; RR 2.08, 95% CI 2.06 to 499.18).

AUTHORS' CONCLUSIONS: The review found promising evidence supporting the use of CHM for primary dysmenorrhoea; however, results are limited by the poor methodological quality of the included trials.

PMID: 17943847 [PubMed - indexed for MEDLINE]

6. [Zhongguo Zhong Xi Yi Jie He Za Zhi. 2006 Aug ;26 \(8\):685-8 16970088 Cit:1](#)

[Effect of erzhi tiangui recipe on ovarian reactivity in elderly sterile women]

Fang Lian, Lin Wang, Jian-wei Zhang

Hospital Affiliated to Shangdong University of TCM, Jinan 250011. f_lian@163.com

OBJECTIVE: To observe the clinical effect of Erzhi Tiangui Recipe (ETR), a traditional Chinese recipe for strengthening Shen and nourishing Tiangui, in improving the ovarian reactivity in elderly sterile women. **METHODS:** Sixty-six elderly sterile women receiving in vitro fertilization pre-embryo transfer (IVF-ET) were randomly divided into two groups: the ETR group treated with ETR plus follicle stimulating hormone (FSH) and the control group treated with FSH alone, 33 cases in each group. Changes of symptoms and the relative parameters were observed, including the dosage of FSH used, the serum hormone levels at different periods, endometrium thickness and arteriopalmus of uterus and ovary on the day of HCG injection, follicle number, follicular oocyte number, mature follicular oocyte rate and fertilization rate, prime embryo rate, and pregnancy rate. Moreover, the correlation of the symptom score of colpoxerosis (CR2) and serum estradiol (E2) level was analyzed after treatment (on the HCG injection day). **RESULTS:** Symptoms of Shen qi-yin deficiency were improved significantly in the ETR group, with the improvement better than that in the control group ($P < 0.05$). The total and daily FSH dosage in the ETR group were lower than those in the control group, showing significant difference between the two groups ($P < 0.05$). The effects were better in the ETR group than those in the control group in increasing serum E2 and endometrium thickness on the HCG injection day, and also in elevating the follicular oocyte number, the mature oocytes rate, the fertilization rate, and the prime embryo rate (all $P < 0.05$). CR2 analysis

showed low negative correlation in both groups ($r = -0.369$ in the ETR group and $r = -0.425$ in the control group), suggesting E2 could be one of the factors but not the only factor for influencing colpoxerosis. And the score of colpoxerosis was lower in the ETR group after treatment than that in the control group ($t = 2.422$, $P < 0.05$). CONCLUSION: ETR combined with FSH can obviously reduce the dosage of FSH used, improve ovarian reactivity and pregnancy rate, and improve the quality of oocytes, the mechanism is possibly related with its effects in improving ovarian reactivity elevating blood estradiol and regulating the hypothalamus-pituitary-ovary axis (HPOA).

Keywords: etr; fsh; oocyte; sterile women; ovarian; group; recipe; hcg; elderly; reactivity; follicular oocyte; women; sterile; hcg injection; control group;

7. *Chin J Integr Med.* 2009 Mar ;15 (1):42-6 19271169

Effect of Quyu Jiedu Granule () on microenvironment of ova in patients with endometriosis.

Fang Lian, Xin-Ling Li, Zhen-Gao Sun, Jian-Wei Zhang, Yan-He Liu, Feng-Mei Ma
Reproductive and Genetic Center of Integrative Medicine, the Affiliated Hospital of Shandong University of Traditional Chinese Medicine, Jinan, 250011, China, f_lian@163.com.

OBJECTIVE: To observe the effect of Quyu Jiedu Granules (, QJG) on the micro-environment of ova in patients with endometriosis (EM). environment METHODS: Twenty EM patients who received in vitro fertilization and embryo transfer (IVF-ET) were randomized equally into a treated group and a control group. Further, 20 patients who received IVF-ET due to oviduct factors were enrolled into a non-endometriosis group. The dosage of gonadotrophic hormone used, the number of ova attained, fertilization rate and clinical pregnancy rate were all observed, and the levels of tumor necrosis factor alpha (TNF-right harpoon over left harpoon) and interleukin 6 (IL-6) in follicular fluid as well as their mRNA expressions in ovarian granular cells were detected by RT-PCR on the very day of ovum attainment. RESULTS: The ova attainment (13.80 ± 6.87) and fertilization rate (0.69 ± 0.31) in the treated group were all higher than the corresponding values in the control group (9.80 ± 5.32 and 0.47 ± 0.22); the follicular fluid contents of TNF-alpha and IL-6 in the treated group were 1.38 ± 0.21 ng/mL and 130.56 ± 12.81 pg/mL, respectively, which were lower than those in the control group (1.98 ± 0.34 ng/mL and 146.83 ± 17.65 pg/mL, respectively). Further, the treated group showed much lower mRNA expressions of TNF-alpha and IL-6 in ovarian granular cells.

CONCLUSIONS: The elevation of TNF-alpha and IL-6 contents in follicular fluid and their mRNA expressions in ovarian granular cells are possibly related to the low quality of ova in EM; QJG might raise the ova quality by reducing TNF-alpha and IL-6 levels to improve the living micro-environment for the ova.

Keywords: ova; endometriosis; tnf-alpha; follicular fluid; harpoon; granular cell; granule; ovarian; treat group; group; ivf; follicular; fertilization; microenvironment; pg/ml;

8. [Zhongguo Zhong Xi Yi Jie He Za Zhi. 2008 Nov ;28 \(11\):977-80 19213337](#)

[Combined therapy of Chinese medicine with in vitro fertilization and embryo transplantation for treatment of polycystic ovarian syndrome]

Fang Lian, Zhen-Gao Sun, Jian-Wei Zhang

Center of Reproduction, Affiliated Hospital of Shandong University of Traditional Chinese Medicine, Jinan. f_lian@163.com

OBJECTIVE: To evaluate the validity of Chinese drugs for reinforcing Shen and regulating Chong channel (RSRCC) on patients with polycystic ovarian syndrome (PCOS) undergoing in vitro fertilization and embryo transplantation (IVF-ET). METHODS: Sixty-four patients with PCOS undergoing IVF-ET were randomly assigned to two groups, the treated group (36 cases) and the control group (28 cases), to the former, Chinese recipe for RSRCC was given additionally. RESULTS: On the human chorionic gonadotrophin (HCG) injecting day, the percentage of three-line sign of endometrium (type A) in the treated group was 75.0%(27/36), which was higher than that in the control group (42.9%, 12/28), showing significant difference between the two groups ($P < 0.01$). The rates of mature oocytes, fertilization, high-qualified embryo rate, clinical pregnancy rate and incidence rate of ovary hyper-stimulating syndrome (OHSS) in the treated group were (76.8 +/- 8.2)%,(73.5 +/- 8.9)%,(89.4 +/- 14.4)% , 36.11%(13/36) and 5.56%(2/36), respectively; whereas those in the control group (64.4 +/- 8.7)%,(68.2 +/- 10.0)%,(79.5 +/- 15.2)% , 21.43%(6/28) and 10.71%(3/28); the dosage of gonadotrophin administered in the treated group was 33.8 +/- 12.5 ampoules, and in the control group 47.6 +/- 18.2 ampoules, statistical significance was shown

between groups in comparing all the above-mentioned parameters ($P < 0.05$, $P < 0.01$). However, the number of oocytes obtained in the two groups was insignificantly different ($P > 0.05$). CONCLUSION: Combined use of Chinese drugs for RSRCC in IVF-ET can reduce the dosage of gonadotrophin administered and raise the clinical pregnant rate.

9. *Zhongguo Zhong Xi Yi Jie He Za Zhi*. 2007 Nov ;27 (11):976-9 18173139

[Clinical study on effect of Erzhi Tiangui Granule in improving the quality of oocytes and leukemia inhibitory factor in follicular fluid of women undergoing in vitro fertilization and embryo transfer]

Fang Lian, Yi-li Teng, Jian-wei Zhang

Affiliated Hospital of Shandong University of TCM, Jinan. f_lian@163.com

OBJECTIVE: To investigate the effects of Erzhi Tiangui Granule (ETG) on the concentration of leukemia inhibitory factor (LIF) in follicular fluid (FF) and quality of oocytes/embryos after in vitro fertilization and embryo transfer (IVF-ET). METHODS: Women undergoing IVF-ET were randomly assigned to two groups: the treated group (42 cases) treated with ETG combined with Western medicine and the control group (38 cases) treated with Western medicine alone. Syndrome of Shen-deficiency, amount of oocytes, rates of mature oocytes, fertilization, cleavage, high-quality embryos and pregnancy, as well as LIF level in FF were observed and compared between the two groups. The relationship of LIF level with mature oocyte rate and high-quality embryo rate was analyzed, respectively. RESULTS: In the treated group after treatment, the syndrome of Shen-deficiency and the above-mentioned indexes tested were improved better than those in the control group, respectively. Correlation analysis showed that the LIF level in FF was positively correlated with the rate of mature oocyte, high-quality embryo and the outcome of pregnancy. CONCLUSION: ETG can distinctively increase the amount of oocyte, elevate the quality of embryo and raise the successful rate of IVF-ET. The mechanism maybe correlated to the increase of LIF level in FF and the activating of microenvironment for its full expression.

10. *Zhongguo Zhong Xi Yi Jie He Za Zhi*. 2006 May ;26 (5):431-4 16883911

[Experimental study on effect of er'zhi tiangui granule in improving quality of

oocyte and its correlation with level of insulin-like growth factor-1R mRNA expression in ovary of mice]

Fang Lian, Zhen-gao Sun, Lin Mu

Reproductive Center, Affiliated Hospital of Shandong University of TCM, Jinan.
flian@chinaivf.com

OBJECTIVE: To explore the mechanism of Er'zhi Tiangui Granule (ETG) in improving the quality of oocyte. **METHODS:** Ninety mice were randomly divided into 6 groups. The number of high-quality oocytes was comparatively observed in the 1st experimental group and the 1st control group; the embryonic cleavage rate was observed in the 2nd experimental group and the 2nd control group and the quantity of insulin-like growth factor-1R mRNA (IGF-1R mRNA) expression in ovarian granular cells was determined by using in situ hybridization in the 3rd experimental group and the 3rd control group. **RESULTS:** The high-quality oocytes rate, the embryonic cleavage rate and the quantity of IGF-1R mRNA expression in the three paired groups was (78 +/- 8)% vs (71 +/- 5%), (88 +/- 3)% vs (83 +/- 5)%, 0.4890 +/- 0.0454 vs 0.4439 +/- 0.0283, respectively. The difference between the experimental groups to the respective control groups was significant (all $P < 0.05$), and positive correlation was shown between the high-quality oocytes rate and the quantity of IGF-1R mRNA expression. **CONCLUSION:** The mechanism of ETG in improving the quality of oocyte may be related with the elevation of IGF-1R mRNA level in ovarian granular cells.

11. A preliminary immunopharmacological study of an antiendometriotic herbal medicine, Keishi-bukuryo-gan (Gui Zhi Fu Ling Wan).

Changes in the specific antiendometrial IgM antibodies in an endometriotic patient, who were treated with leuproride acetate and in turn with Keishi-bukuyogan, were investigated by the flowcytometric analysis which was developed in our laboratory. The oriental therapy decreased the specific IgM antibody titer gradually and kept the patient symptom-free for more than 7 months without any suppression of serum CA125 and estradiol levels. On the other hand, leuproride acetate therapy suppressed both serum CA125 and serum estradiol levels but not the IgM antibody titer. The results suggest that the specific antiendometrial IgM autoantibody could be a pathogenic molecule in endometriosis and it could also serve as a clinical marker for the oriental therapy of endometriosis.

Tanaka T; Mizuno K; Umesaki N; Ogita S Department of Obstetrics & Gynecology, Osaka City University Medical School, Japan.
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12. Chinese Herbs increase ATP production and antioxidants

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Enhancement of ATP generation capacity, antioxidant activity and immunomodulatory activities by Chinese Yang and Yin tonifying herbs

Kam Ming Kocorresponding author¹ and Hoi Yan Leung¹

¹Department of Biochemistry, Hong Kong University of Science and Technology, Clear Water Bay, Hong Kong, China

corresponding authorCorresponding author.

Kam Ming Ko: bcrko@ust.hk; Hoi Yan Leung: bclhy@ust.hk

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Abstract

Chinese tonifying herbs such as Herba Cistanche, Ganoderma and Cordyceps, which possess antioxidant and/or immunomodulatory activities, can be useful in the prevention and treatment of age-related diseases. Pharmacological studies on Yang and Yin tonifying herbs suggest that Yang tonifying herbs stimulate mitochondrial adenosine triphosphate (ATP) generation, presumably through the intermediacy of reactive oxidant species, leading to the enhancement of cellular/mitochondrial antioxidant status. Yin tonifying herbs, however, apart from possessing antioxidant properties, exert mainly immunomodulatory functions that may boost a weak immune system and may also suppress overreactive immune responses. The abilities of Yang and Yin Chinese tonifying herbs to enhance ATP generation and to exhibit antioxidant and/or immunomodulatory actions are the pharmacological basis for their beneficial effects on the retardation of aging.

Background

Aging is a process of bodily change with time, leading to increased susceptibility to disease, and ultimately death. Because reactive oxidant species (ROS) and immune dysfunction are major causes of age-related diseases [1-3], the maintenance of antioxidant and immune fitness is a rational approach to preventive health care. Accumulation of ROS-induced oxidative damage to DNA, proteins, and other macromolecules has been regarded as a major endogenous cause of aging [1]. In addition to ROS-mediated cellular damage, aging was found to be associated with immune senescence, attributable at least partly to the loss of T lymphocyte functions [2,3]. Such loss increases the prevalence of infectious diseases in the elderly. With advances in modern medical research techniques, research on age-related chronic illnesses has become intense, in the quest for valuable preventive and therapeutic measures. Humans have been making continuous efforts to fight aging. As Chinese medicine has always emphasized the prolongation of a healthy lifespan, many Chinese

tonifying herbs have long been used to safeguard health and to delay the onset of senility.

Under both normal and pathological conditions, ROS are generated in all cells undergoing aerobic metabolism, particularly from mitochondria. The cell possesses two distinct antioxidant defense systems to counteract damaging ROS: (1) enzymatic antioxidants such as catalase, superoxide dismutase (SOD), glutathione peroxidase and other related enzymes/molecules, and (2) non-enzymatic antioxidants such as ascorbic acid (vitamin C), α -tocopherol (vitamin E) and β -carotene. To achieve optimal antioxidant fitness, every component of the antioxidant defense system should function optimally because antioxidants must work together in a synergistic manner. Chinese tonifying herbs have been shown to possess both in vitro and in vivo antioxidant activities [4,5].

The immune system fights against 'foreign invaders' such as bacteria, viruses, fungi, yeasts and parasites. The humoral and cell-mediated immune responses show great competence in dealing with intruders. Moreover, the surveillance function of the immune system tends to prevent cancers, particularly in old age. However, an overreactive or imbalanced immune system can cause allergies or autoimmune disorders. A well-constituted and balanced immune system is thus crucial for safeguarding health. Chinese tonifying herbs have been shown to stimulate or suppress the cell-mediated immune response both in vitro and in vivo [6].

The importance of disease prevention has been recognized by Chinese medicine through experience accumulated over centuries. Many Chinese tonifying herbs have long been used for safeguarding health and for delaying the onset of senility. According to Chinese medicine theories, tonifying herbs prescribed for various symptoms of ill-health are generally classified into four categories on the basis of their health-promoting actions, namely 'Yang-invigorating', the 'Qi-invigorating', the 'Yin-nourishing' and the 'Blood-enriching' herbs [7]. The 'Qi-invigorating' and 'Blood-enriching' herbs are of Yang and Yin characteristics respectively. Chinese medicine theories suggest that a balance of Yin and Yang is essential to sustain optimal body function [8]. From a modern medical perspective, the maintenance of Yin and Yang in harmony may be described as the attainment of bodily homeostasis. The long-known antagonistic relationship between parasympathetic and sympathetic neural activities affords an example of both a phenomenon well-recognized by Western medicine and the Yin/Yang balance. A recent psychophysiological investigation in humans revealed an association between decreased parasympathetic or sympathetic activities with deficiencies of Yin or Yang respectively [9].

The theoretical framework of Chinese medicine is based on the Chinese cultural fabrics and clinical experience, while modern Western medicine has been established on the basis of laboratory and clinical investigations [10]. As the two distinct medical systems are complementary, bridging of the knowledge gap between Chinese and Western medicine is essential for their integration, in clinical practice, for disease prevention and treatment. Expounding Chinese medicinal theories in modern scientific terms to a Western audience facilitates communication between practitioners of the two systems.

In our earlier studies, we found that tonifying herbs with Yang or Yin properties were associated with antioxidant and immunostimulatory activities respectively [4]. Recent studies indicated that only Yang tonifying herbs (not Yin tonifying herbs) enhanced mitochondrial ATP generation capacity in mouse hearts [11]. We therefore suggest that

Yang tonifying herbs enhance mitochondrial ATP generation, while Yin tonifying herbs are associated with immunomodulatory activities. In this mini-review, we summarize the abilities of Yang and Yin tonifying herbs to enhance ATP generation capacity, and to potentiate antioxidant and/or immunomodulatory actions, in an effort to characterize their respective pharmacological properties.

Enhancement of ATP generation by Yang tonifying herbs

In Chinese medicinal theories, Yang is a manifestation of body functions supported by various organs. A 'Yang-invigorating' action therefore involves the enhancement of bodily functions in general and cellular activities that consume ATP in particular. The mitochondrion is responsible for the generation of ATP through oxidative metabolism. To establish the pharmacological basis of 'Yang-invigorating' action, we have recently investigated the effect of Yang herbs on ATP generation capacity in heart homogenates prepared from mice that were pretreated with methanolic extracts of herbs [11].

Tonifying herbs from other functional categories were examined for comparison. While Chinese herbs are usually extracted by water for human oral consumption, water was replaced by methanol in our study for convenience in the processing and storage of samples. Yang herbs invariably enhanced myocardial ATP generation, with stimulation ranging from 20–130%. *Herba Cynomorii* and *Semen Cuscutae* were the most potent herbs examined. By contrast, none of the Yin herbs enhanced ATP generation; some Yin herbs even suppressed ATP generation slightly (Table 1). A preliminary mechanistic study indicated that Yang herbs may speed up ATP synthesis by increasing mitochondrial electron transport [11].

Effect of Yang and Yin tonifying herbs on myocardial ATP generation capacity in mice *ex vivo*

Correlation between enhancement of ATP generation capacity and antioxidative capacity

Mitochondrial oxidative phosphorylation generates ROS as byproducts. Highly reactive chemically, ROS attack cellular structures located near the sites where ROS are generated. Mitochondrial DNA, proteins, and lipids in the inner membrane of mitochondria are thus vulnerable to oxidative damage [12], resulting in generalized organelle dysfunction, defective mitochondrial biosynthesis and poor energy metabolism [13].

Under normal physiological conditions, the mitochondrial antioxidant defense system adequately handles the potentially detrimental effects of ROS derived from energy metabolism [14]. When a functional imbalance between ROS levels and antioxidant concentrations caused by various disease states and/or aging occurs, age-related disorders such as cancer, cardiovascular diseases, brain dysfunction, or cataract may occur [15]. Antioxidant supplementation, particularly from herbal extracts, has become a trend in preventive health care.

Using an oxygen radical absorbance capacity assay, Ou et al. recently compared the free radical scavenging (i.e. antioxidant) activities of Yang and Yin herbs [16]. The results indicated that Yin herbs generally possessed higher antioxidant activities than Yang herbs and that the antioxidant potencies correlated well with the amounts of total phenolic compounds in the herbs. The authors suggested an analogy between Yin/Yang balance and antioxidation/oxidation in energy metabolism. These findings of higher antioxidant activities in Yin herbs as compared with those in Yang herbs do not agree with the findings from one of our earlier studies which showed that most of the Yang herbs possessed a more potent 1,1-diphenylpicrylhydrazyl radical-scavenging action than other tonifying herbs [4] (Table 2). Although the use of different herbal extraction

methods and distinct antioxidant assays precludes direct comparison of the two studies, the discrepancy might be due to the selection of almost completely different sets of Yin and Yang herbs for testing in the two studies. Our study focused on herbs used for safeguarding health (i.e. herbs used for tonifying purposes) (Tables 2, Table 3 of reference [17]). Ou et al. probably used a selection criterion based on the general Yin and Yang properties of the herbs instead of their Yin-tonifying and Yang-tonifying actions [16]. Szeto and Benzie, using the same set of herbs described in Ou et al. to examine possible protective effects on DNA oxidative damage, found that the Yang herbs showed an antioxidant effect superior to that of Yin herbs [5].

Antioxidant activities of Yang tonifying herbs

Several Yang herbs have been shown to possess antioxidant activities both in vitro and in vivo (Table 4). In vitro free radical-scavenging activities were detected in herbal extracts prepared from *Herba Epimedii* [4,18], *Radix Dipsaci* [4,16], *Fructus Psoraleae* [4], *Semen Cuscutae* [16], *Herba Cistanche* [4,16,18], *Cortex Eucommiae* [19] and *Rhizoma Cibotii* [4,16]. Aqueous extracts of *Rhizoma Drynariae* and *Cortex Eucommiae* were found to inhibit oxidant production from rat osteoblasts [20], and also inhibited biomolecular oxidative damage [21]. Active ingredients (bakuchiol, isobavachin and isobavachalcone) from *Fructus Psoraleae* inhibited the NADPH-dependent peroxidation of rat microsomal and mitochondrial lipids in vitro [22]. An ethanolic extract of *Radix Dipsaci* enhanced the antioxidant status of blood and liver in rodents [23] and a *Radix Morindae* extract increased blood antioxidant enzyme activities in diabetic rats [24]. Phenylethanoids isolated from *Herba Cistanche* were found to prevent cell damage induced by in vitro and in vivo exposure to carbon tetrachloride in rats [25]. A recent study from our laboratory indicated that pretreatment with the methanolic extract of *Herba Cistanche* protected against ischemia-reperfusion injury in rat hearts ex vivo and enhanced mitochondrial ATP generation in the rat hearts ex vivo and H9c2 cells in situ. The ATP-stimulating action was possibly due to enhanced oxidative phosphorylation caused by increases in the activities of complexes I and III [26]. As good body function requires a large amount of energy and antioxidant defense is essential in sustaining mitochondrial ATP production [27], the antioxidant activities of Yang herbs may safeguard ATP generation, particularly under conditions of upregulated cellular activities.

Antioxidant activities of Yang tonifying herbs

Antioxidant activities of Yin tonifying herbs

Methanolic extracts of both *Fructus Ligustri* and *Herba Ecliptae* were found to enhance hepatic glutathione (GSH) regeneration capacity in rats [4,28]. The enhancement of hepatic GSH regeneration capacity by *Fructus Ligustri* was associated with a hepatoprotective action against carbon tetrachloride toxicity [28]. Activity-directed fractionation of *Fructus Ligustri* indicated that the hepatoprotective principle(s) resided mainly in the oleanolic acid-enriched butanol and chloroform fractions [28]. Moreover, our recent studies showed that both short and long term pretreatment with oleanolic acid protected against myocardial ischemia-reperfusion injury in rats [29,30]. It was suggested that the cardioprotection afforded by oleanolic acid pretreatment was related to the enhancement of mitochondrial antioxidant mechanism mediated by GSH and α -tocopherol [29]. Both experimental and clinical investigations indicated that the antioxidant status influenced immunocompetence, particularly under conditions of stress such as physical exercises or chronic diseases [31]. The antioxidant activities of Yin tonifying herbs may positively influence immunostimulatory activities.

Experimental studies on a 'Yang-invigorating' herbal formula

A 'Yang-invigorating' herbal formula named VI-28 has been shown to produce 'Yang-invigorating' effects [32] and enhance red cell antioxidant status, particularly Cu-Zn-

superoxide dismutase (SOD) activity, in elderly male human subjects [33]. This herbal formula is comprised of Radix Ginseng, Cornu Cervi, Cordyceps, Semen Allii, Fructus Cnidii, Fructus Evodiae and Rhizoma Laemferiae. Recently we investigated the effects of long-term VI-28 treatment on red cell Cu-Zn-SOD activity, mitochondrial functional ability, and antioxidant levels, in various tissues of rats of both sexes [34]. The results indicated that VI-28 treatment increased red cell Cu-Zn-SOD activity and mitochondrial ATP generation capacity, increased the levels of reduced GSH and α -tocopherol, and reduced Mn-SOD activities. The enhancement of ATP generation by VI-28 increased mitochondrial ROS production, resulting in the upregulation of mitochondrial antioxidant mechanism. The VI-28-induced increase in mitochondrial antioxidant capacity in various tissues was evidenced by a significant reduction in ROS generation. Given that cellular energy status and mitochondrial ROS generation are factors critically involved in aging, the dual effect of 'Yang-invigoration' produced by VI-28 may have clinical implications in the prevention of age-related diseases.

Immunomodulatory activities of Yin tonifying herbs

It was suggested that the proper functioning of the immune system requires dynamic interactions between Yang and Yin. And while the antigen-nonspecific immune response is associated with Yang, the antigen-specific response is related to Yin [35]. One of our earlier studies investigated antioxidant and immunomodulatory activities in different categories of tonifying herbs. The results showed that 6 and 7 of a total of 8 Yin herbs tested potentiated concanavalin A (Con A)-stimulated splenocyte proliferation (an antigen-specific response) in mice in vitro and ex vivo respectively. By contrast, only 3 of 9 Yang herbs tested showed a similar enhancement of the Con A-stimulated immune response [4] (Table 2).

Among the Yin herbs, the methanolic extract of Fructus Ligustri yielded the most robust immunostimulatory action in mouse splenocytes [4]. Differential extraction of Fructus Ligustri by solvents of increasing polarity indicated that the immunostimulatory activity resided mainly in the petroleum ether fraction [36]. Oleanolic acid, an immunomodulatory triterpenoid commonly found in herbs including Fructus ligustri [37,38], was undetectable in this fraction [36]. Currently, activity-directed fractionation of the petroleum ether extract of Fructus Ligustri is under way in our laboratory. Various immunomodulatory actions of Yin tonifying herbs, and the active ingredients of the herbs, have been reported in other studies (Table 5). An aqueous extract of Radix Asparagi was found to inhibit tissue necrosis factor- α (TNF- α) secretion by suppressing Interleukin (IL)-2 secretion from astrocytes, implicating that the extract might exhibit anti-inflammatory activity in the central nervous system [39]. Both the crude aqueous extract and the two active ingredients (ruscogenin and ophiopogonin D) of Radix Ophiopogonis produced anti-inflammatory effects in rodents [40]. While the aqueous extract inhibited xylene-induced ear swelling and carrageenan-induced paw edema in mice, it also suppressed carrageenan-induced pleural leukocyte migration in rats, and the zymosan-evoked migration of peritoneal total leukocytes and neutrophils in mice. Treatments with ruscogenin and ophiopogonin D decreased zymosan-induced peritoneal leukocyte migration in mice and reduced the phorbol-12-myristate-13 acetate-induced adhesion of HL60 cells to ECV304 cells [40]. Several sesquiterpenes isolated from Herba Dendrobii were found to exhibit immunomodulatory activity by exerting comitogenic effects on Con A and lipopolysaccharide-stimulated mouse splenocytes [41,42]. It has recently been reported that an ethanolic extract of black rice (the fruit of *Oryza sativa*) showed anti-asthmatic effects in a mouse model [43]. Treatment with the ethanolic extract of black rice reduced the number of eosinophils in bronchoalveolar lavage fluid, alleviated the airway hyper-response, and decreased the extent of airway inflammation in ovalbumin

(OVA)-immunized and -aerolized mice challenged with OVA. Moreover, the ethanolic extract treatment decreased interferon- γ (INF- γ), IL-4, IL-5 and IL-13 levels in the supernatants of cultured splenocytes and suppressed the plasma levels of OVA-specific immunoglobulin (Ig)G, IgG2 α , IgG1 and total IgE in OVA-immunized and -challenged mice [43]. Clinical investigations indicated that intramuscular injection of undiluted Fructus Ligustri extract at a dose of 2–4 ml once or twice daily could prevent leucopenia caused by chemotherapy or radiotherapy. Fructus Ligustri treatment normalized white blood cell counts, thereby increasing tolerance to chemo/radiotherapy [44]. Oral administration of Fructus Ligustri tablets at a daily dose of 50 g equivalence of crude herb was found to ameliorate the symptoms of chronic bronchitis [44]. A herbal formula comprising Fructus Ligustri, Radix Scutellariae, Radix Astragalus and Eupolyphaga et polyphae was found to alleviate symptoms and improve immune function in HIV/AIDS patients [45].

Immunomodulatory activities of Yin tonifying herbs

Ganoderma – A 'Fu Zheng' tonifying herb

Ganoderma, another Yin tonifying herb with immunomodulatory effects, is widely consumed by the Chinese people who believe that it promotes health and longevity, lowers the risk of cancer and heart diseases and boosts the immune system [46]. In Chinese medicine, Ganoderma is regarded as a very potent herb for 'Fu Zheng', a Chinese medicine concept comparable to immunotherapy/immunomodulation in Western medicine. While Ganoderma is traditionally used to increase the resistance of the body immune system to pathogens and to restore normal body functions, the herb has now also been used to decrease the side effects of Western medical procedures, such as surgery, radiotherapy and chemotherapy which often weaken the immune system. The anti-cancer/immunomodulatory effects of Ganoderma were associated with triterpenes [47], polysaccharides [48,49] or immunomodulatory proteins [50] through mechanisms involving inhibition of DNA polymerase [51], inhibition of post-translational modification of the Ras oncoprotein [52] or the stimulation of cytokine production [53]. Recent studies on the immunomodulatory activities of Ganoderma indicated that Ganoderma extract stimulated the proliferation of human peripheral blood mononuclear cells and raised the levels of mRNAs encoding Th1 and Th2 cytokines in these cells [54]. Moreover, polysaccharides of Ganoderma activated mouse splenic B cells and induced these cells to differentiate into IgM-secreting plasma cells. This process was dependent on the polysaccharide-mediated induction of Blimp-1, a master regulator capable of triggering a cascade of gene expression during plasmacytic differentiation [55]. In human peripheral B lymphocytes, the Ganoderma polysaccharide fraction enhanced antibody secretion and induced the production of Blimp-1 mRNA, though it failed to induce lymphocyte differentiation [55].

In addition to immunomodulating activities, Ganoderma possesses in vivo antioxidant potential, another aspect of Yin tonifying action. Treatment with Ganoderma extract was found to enhance the hydroxyl radical scavenging activity of rabbit blood plasma [56,57]. Ganoderma acted by stimulating cellular and mitochondrial SOD activities, thereby enhancing the antioxidant capacity of the body [58]. It was shown that an intraperitoneal injection of Ganoderma extract following a lethal dose of cobalt X-ray radiation caused a marked prolongation of survival time in mice [59]. Pretreatment with Ganoderma extract also markedly protected against carbon tetrachloride-induced hepatic damage and the associated impairment in hepatic antioxidant status [60].

Cordyceps – A Yin/Yang tonifying herb

Cordyceps, a premium Chinese tonifying herb which replenishes the 'kidney' and soothes the 'lung', is prescribed for the treatment of a host of disorders, including

hyposexualities, hyperglycemia, hyperlipidemia, asthenia after illness, respiratory diseases, renal disorders, liver and heart diseases [61]. Cordyceps is regarded as a tonifying herb with both 'Yin-nourishing' and 'Yang-invigorating' actions. Pharmacological studies have shown that Cordyceps possesses a wide spectrum of biological activities including antioxidation [61-64], immunopotentiality [65-68], anti-tumorigenesis [68-71], anti-inflammation [72] and stimulation of testosterone biosynthesis [73]. We have recently investigated the effects of wild and cultured Cordyceps on Con A-stimulated splenocytes (an in vitro bioassay for Yin tonifying action) and myocardial ATP generation capacity (an ex vivo bioassay for Yang tonifying action) [74]. The results indicated that methanolic extracts of wild and cultured Cordyceps enhanced both the Con A-stimulated splenocyte proliferation in vitro and myocardial mitochondrial ATP generation ex vivo in mice, with no significant difference in potencies when the two types of Cordyceps were compared. While the immunopotentiating effect was associated with an increase in IL2 production, the stimulation of myocardial ATP generation was paralleled by an enhancement in mitochondrial electron transport. When compared with typical Yin and Yang tonifying herbs (Fructus Ligustri and Herba Cynomorii respectively), Cordyceps was found to possess both Yin and Yang tonifying actions, with a lower potency in both modes of action. The observation of both immunopotentiating and ATP-enhancing activities in Cordyceps extracts further supports the pharmacological basis of Yin and Yang tonifying herbs in Chinese medicine.

Conclusion

Yang tonifying herbs stimulate mitochondrial ATP generation, leading to the enhancement of cellular/mitochondrial antioxidant status, presumably through the intermediacy of ROS. Yin tonifying herbs, which also possess antioxidant properties, are mainly immunomodulatory, thereby boosting weak immune functions and suppressing overreactive or unbalanced immune responses. Cordyceps, highly regarded as a tonifying herb with a dual action of Yin and Yang, stimulates mitochondrial ATP generation and enhances cellular immune responses. Given that impairment in mitochondrial functional ability and antioxidant status, and a decline in immunocompetence, are believed to be critically involved in the development of age-related diseases and the aging process, the abilities of Yang and Yin tonifying herbs to enhance ATP generation capacity and to produce antioxidant and immunomodulatory actions are beneficial for safeguarding health and delaying the onset of senility (Figure 1). While animal models may be used for testing working hypotheses on Yang and Yin tonifying actions, clinical studies, using Yang and Yin tonifying herbs and/or defined chemicals isolated from the herbs or synthesized in the laboratory, on age-related variations in antioxidant and immune function, would be of considerable value.

13. Measuring the Effectiveness of Chinese Herbal Medicine in Improving Female Fertility

Keywords: Infertility, Chinese herbal medicine, ultrasound, hormone levels.

Aim: To determine the relationship between female fertility indicators and the administration of Chinese herbal medicine (CHM).

Design: A prospective cohort clinical study to measure accepted bio-medical

factors that affect female fertility and to determine if CHM can improve these factors as well as pregnancy outcome.

Setting: A private practice specializing in treating infertility with traditional Chinese medicine (TCM). The study took place between November 2003 and December 2004.
Patient(s): Fifty women with the Western medical diagnosis of unexplained infertility.

Interventions: One monitored menstrual cycle measuring pre-treatment fertility factors, followed by treatment with Chinese herbal medicine and subsequent measurement of the changes in the same fertility factors.

Results: Significant differences were observed between the two time points for the majority of factors measured. Pregnancies in the sample group recorded 6 months after commencement of the last treatment were 28, with 11 live births and 7 miscarriages.

Conclusion: The study outcome demonstrates that using Chinese herbal medicine results in higher success rates of pregnancy, with no patient side-effects and a reduction in the category of patients conventionally classified as having unexplained infertility.

Introduction

The research question this study seeks to answer is “Does administering Chinese herbal medicine (CHM) improve the physiological factors affecting human female fertility?” The hypothesis is that administering CHM improves the main physiological factors affecting human female fertility and therefore also the pregnancy rate. These factors are ovarian follicle number and size, uterine endometrium thickness, uterine artery haemodynamics, serum follicle stimulating hormone (FSH), serum progesterone levels and corpus luteum vascularity.

Research aims and objectives

1. Establish a sample group of 50 new patients registering for fertility treatment at a London natural health fertility clinic.
2. Test and record a predetermined group of twelve measurements prior to treatment during one menstrual cycle.
3. Administer CHM in capsule form for one menstrual cycle.
4. Re-test the same parameters in the third cycle of treatment, continue to administer CHM for six months (or until pregnancy is achieved if this occurs in less than six months). Follow up six months after the beginning of the last patient's treatment
5. To determine the number of pregnancies achieved.
6. Analyze results and discuss findings.
7. Draw conclusions and make recommendations for further practice and study.

Methodology

The challenge for any investigative method when applied to traditional Chinese medicine (TCM) is that in everyday practice, the same disease in different patients will have a different treatment principle and herbal prescription. The information collected from the traditional Chinese examination and assessment determines a diagnosis based on pattern differentiation and hence a treatment principle and formula which is individualized for each patient. In our treatment of infertility there is, in addition, a weekly modification of each patient's formula. As there is thus no standardization of formulae for

patients it is not appropriate to discuss the formulae themselves in this study, but rather to simply study the effects of Chinese herbal medicine treatment on female fertility.

The method chosen was a prospective cohort primary study using a sample group of patients registered with the clinic for TCM infertility treatment.

Patients were selected for the study on the basis that they had no Western medical condition which might have affected their fertility. In other words they were described in Western medical terms as having unexplained infertility. They also entered the study on the condition that data obtained in the course of their treatment could be used in the study anonymously.

Trevor A. Wing & Elke S. Sedlmeier

14. Preventive and therapeutic effects of Bushen Huoxue Recipe on autoimmune premature ovarian failure in mice

Dong L, Jiang L, Men W, Zhu NS. <http://www.ncbi.nlm.nih.gov/pubmed/18334152>

Department of Gynecology, Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai 200437, China; E-mail: dongli888@yahoo.com.

Objective: To investigate the preventive effect of Bushen Huoxue Recipe (BSHXR), a compound traditional Chinese herbal medicine, on autoimmune premature ovarian failure (POF) in mice. **Methods:** Ovarian antigen was prepared with the ovarian tissue of female BALB/c mice. A mouse model of POF was established by immunization injection of the ovarian antigen of isotype female mice on multiple subcutaneous sites and two posterior soles. The POF mice were treated with BSHXR after the first and third immunization. The levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH) and estradiol (E2) in peripheral blood were detected by enzyme linked immunosorbent assay. **Results:** Lymphocyte infiltration was appeared in ovarian stroma of POF mice. The levels of FSH and LH were evaluated and the E(2) level was decreased significantly ($P < 0.05$). BSHXR could reduce the increased levels of FSH and LH, increase the level of E(2) and the number of growing and mature follicles. The efficacy of early treatment was better than that of late treatment. **Conclusion:** BSHXR can recover ovarian function in POF mice mainly by regulating the indiscriminate hormone level, and BSHXR has preventive effect on autoimmune POF in mice.

15. Protective effect of zuogui pill on ovarian autoimmune injury

Zhu L, Luo SP, Xu LM.

Department of TCM, Southern Medical University, Guangzhou.

OBJECTIVE: To probe the effect of Zuogui pill (ZGP), a Chinese compound recipe for tonifying Shen, on ovarian function in mice with premature ovarian failure (POF). **METHODS:** BALB/C female mice model of POF was established by multiple sites subcutaneous injection of ovarian antigen elicited with ovarian tissue of SD female rats, and treated with ZGP at different time points in the modeling, with prednisone as positive control. The levels of follicle-stimulating hormone (FSH) and estradiol (E2) in peripheral

blood were measured with radioimmunoassay, and ovarian antibody (AoAb) was determined by enzyme linked immunosorbent assay. The mRNA expression of ovarian growth and differentiation factor-9 was detected with in situ hybridization. RESULTS: POF model mice manifested such abnormalities as increased FSH, decreased E2, and positive AoAb in peripheral blood, with lymphocytes infiltration in ovarian mesenchyma, reduction of GDF-9 mRNA positive oocytes, and decrease of growing and mature follicles. ZGP could reduce the increase of FSH, increase the level of E2, inhibit the production of AoAb, raise the GDF-9 mRNA positive cells of oocytes, increase the number of growing and mature follicles. The clinical efficacy was more significant in early stage than in advanced stage. CONCLUSION: ZGP can improve immune inflammatory injury of ovary, and shows therapeutic effect on POF.

16. Research into Chinese herbal medicine and ovarian dysfunction

9 separate studies

(1) The effectiveness of a Chinese formula called Tian gui fang in comparison with metformin was tested on patients with polycystic ovarian syndrome [PCOS]. The patients were divided into two groups and either Tian gui fang or metformin was administered for three months. After treatment, 4 out of the 8 patients on metformin had restoration of menstrual cyclicity, and two of them had a double phase BBT. The testosterone levels had decreased. No other measures changed. In the group that received the Chinese medicine, 6 patients out of 8 had a restored cycle as well as a double phase BBT. Testosterone and the body mass index (BMI) decreased significantly. The authors conclude that both therapies can induce ovulation but that Chinese herbal medicine has a higher efficacy in restoring ovulation and normal BBT measures.

Hou J, Yu J, Wei M. [Study on treatment of hyperandrogenism and hyperinsulinism in polycystic ovary syndrome with chinese herbal formula tian gui fang] . Zhongguo Zhong Xi Jie he Za Zhi. 2000; 20 (8):589.

(2)The effectiveness of a Chinese herbal formulary was tested on patients with high LH levels due to polycystic ovary syndrome. Eight weeks of treatment with Chinese herbal medicine significantly reduced plasma LH.

Ushiroyama T, Ikeda A, Sakai M, Hosotani T, Suzuki Y, Tsubokura S, Ueki M. Effects of unkei-to, an herbal medicine, on endocrine function and ovulation in women with high basal levels of luteinizing hormone secretion. J Reprod Med. 2001 May; 46(5):451-6.

(3) In Japan, a Chinese herbal formulary was tested on patients with polycystic ovarian disease [PCOD] to find an effective treatment without side effects that could be used instead of clomiphene citrate or gonadotropin therapy. After a course of treatment, the FSH/ LH ratio had significantly decreased, and the ovulatory rate was 70.6%. Serum testosterone did not change during treatment. The authors conclude that the Chinese formula may be useful for the treatment of anovulation in PCOS patients.

Sakai A, Kondo Z, Kamei K, Izumi S, Sumi K. Induction of ovulation by Sairei-to for polycystic ovary syndrome patients. Endocr J. 1999 Feb; 46(1):217-20.

(4) A case study from Taiwan discusses the effective treatment of premature ovarian failure using Chinese herbal medicine. Clomiphene citrate therapy over 8 months had not changed the FSH and LH levels from the postmenopausal range. A course of 4 months treatment with Chinese herbal medicine based on Zuo gui wan induced an ovulation, and the patient fell pregnant. The authors conclude that Chinese herbal medicine can restore ovarian function effectively and promptly and offers another option for treating infertility in patients with premature ovarian failure.

Chao SL, Huang LW, Yen HR. Pregnancy in premature ovarian failure after therapy using Chinese herbal medicine. A case study. *Chang Gung Medical Journal* 2003 Jun; 26(6): 449-52.

(5) At Shanghai medical university, the effectiveness of Chinese medical herbs from the category of yin supplementing were tested on 35 patients with polycystic anovulation. The patients were treated for three months, and a variety of tests were carried out before and after the course of treatment. Testosterone levels lowered significantly. In 59.7% of patients and a regular cycle was reestablished. 41.2% of women became pregnant. The authors conclude that Kidney Yin nourishing herbs could provide a good microcircumstance for ovarian follicular growth, which results in ovulation and pregnancy.

Zhou LR, Yu J. [Clinical observation on treatment of hyperinsulinemia and hyperandrogenism anovulatory patient with replenishing kidney-yin drugs] *Zhongguo Zhong Xi Yi Jie He Za Zhi*. 1996 Sep; 16(9): 515-8.

(6) Hachimijiogan, a Chinese herbal formula (Liu wei dihuang wan + rou gui, yin yang huo, huang qi), was shown in one study to benefit female infertility due to pituitary dysfunction. Two infertile women (one with and one without a pituitary adenoma) who were resistant to medical treatment, were given Hachimijiogan which subsequently reduced the serum prolactin level, and resulted in a normal ovulatory cycle and pregnancy, without side effects.

Usuki S; Kubota S; Usuki Y. Treatment with hachimijiogan, a non-ergot Chinese herbal medicine, in two hyperprolactinemic infertile women. *Acta Obstet Gynecol Scand* 1989, 68 (5) p475-8.

(7) In another study looking at pituitary dysfunction causing infertility, 27 women were given the same formulae as discussed above. 6 of the women had amenorrhea. In 15 patients, the prolactin levels dropped to a healthy range, and remained low 6 months after the course of treatment. Four patients with amenorrhea ovulated. Eleven patients conceived and delivered a healthy baby. In three women, the prolactin level did not lower. The authors conclude that a modification of Liuwei di huang wan can be a safe and effective treatment for hyperprolactinemic women.

Usuki S, Usuki Y. Hachimijiogan treatment is effective in the management of infertile women with hyperprolactinemia or bromocriptine-resistant hyperprolactinemia. *American Journal of Chinese Medicine* 1989; 17 (3-4):225-41.

(8) In one study of female infertility, 53 patients with luteal phase defect (LPD) were treated with different Chinese medicinal herbs at different phases of menstrual cycle. The patients were treated for three menstrual cycles and there was significant improvement in the luteal phase of endometrium, and a tendency for normalization of the wave forms and

its amplitude after the treatment. The findings suggested that Chinese herbal medicines are capable of replenishing the Kidney and regulate the hypothalamus-pituitary-ovarian axis and thus improve the luteal function. Among the 53 cases, 22 (41.5%) conceived but 68.18% of them required other measures to preserve the pregnancy.

Zhang HY; Yu XZ; Wang GL Preliminary report of the treatment of luteal phase defect by replenishing kidney. An analysis of 53 cases. *Zhongguo Zhong Xi Yi Jie He Za zhi* Aug 1992, 12 (8) p473-4, 452-3.

(9) Women with normal menstrual cycles but low basal body temperature and progesterone levels (luteal insufficiency) were effectively treated with a Chinese herbal formulary called Dang guishao yao tang, with no observed side effects.

Usuki S, Higa TN, Soreya K. The improvement of luteal insufficiency in fecund women by tokishakuyakusan treatment . *Am J ChinMed*. 2002; 30(2-3):327-38.

17. RESEARCH INTO RECURRENT MISCARRIAGE & CHINESE HERBAL MEDICINE

Shanghai Gynaecology & Obstetrics Department of Shanghai Medical University.

In 40 women with threatened abortion and a history of miscarriage, blood test showed threatened abortion (TA), compared to the blood test of normal pregnant women (The plasma beta-EP level in TA was significantly higher than that in normal pregnant women, $P < 0.01$. On the contrary, plasma GnRH, HCG and P4 were obviously lower in TA as compared with those of the normal cases, $P < 0.01$.) After treatment with Chinese herbal medicine that supported reproduction and blood circulation and protected the foetus, 36 of the 40 patients continued their pregnancy without symptoms of TA, and the above-mentioned four criteria measured at 10-12th week of gestation were similar to those of normal cases, $P > 0.05$. The authors concluded that Chinese herbal Medicine can regulate plasma beta-EP and placental endocrine function in threatened abortion in women with a history of recurrent miscarriage.

Sun F, Yu J. [Effect of TCM on plasma beta-endorphin and placental endocrine in threatened abortion] *Zhongguo Zhong Xi Yi Jie He Za Zhi*. 1999 Feb; 19 (2):87-9.

(2) A study in Japan showed that recurrent miscarriages with an immunological component (rejection of the foetus as foreign) benefit positively to the treatment with Chinese herbal medicine. Twelve patients with recurrent abortion who had shown positive anti-phospholipid antibodies were treated through the administration of a Japanese modified traditional Chinese herbal medicine Sairei-To (Cai ling Tang). The patients had experienced a total of 27 spontaneous abortions in their previous pregnancies and had no other pregnancy history except for one patient. The patients were treated with 9.0 g of Sairei-To per day before their next pregnancy. The positive value of antiphospholipid antibodies returned to negative in 9 patients out of 12 patients through the treatment. Out of 12 patients, 10 patients continued their new pregnancy uneventfully, and they delivered an offspring (Success rate: 83.3%). Thus, the current treatment was considered to be an effective therapy for patients with recurrent abortion whose miscarriage is immune related (positive anti-phospholipid antibodies).

Takakuwa K, Yasuda M, Hataya I, Sekizuka N, Tamura M, Arakawa M, Higashino M, Hasegawa I, Tanaka K. Treatment for patients with recurrent abortion with positive

antiphospholipid antibodies using a traditional Chinese herbal medicine. *J Med.* 1996; 24(5):489-94.

18. An experimental study on inhibitory effect of Chinese medicine tai-bao on antisperm antibody

OBJECTIVE: To investigate whether Chinese medicine Tai-bao could inhibit antisperm antibody in experimental mice.

METHODS: The experimental immunoinfertility mice were due to antisperm antibody induced by injection of human sperm membrane antigens. The experimental immunoinfertile mice used in the present study were divided into four groups including Tai-bao high dose group (46.8 g.kg-1.d-1), Tai-bao low dose group (31.2 g.kg-1.d-1), prednisone group and normal saline group. The enzyme linked immune sorbent assay (ELISA) and microcytotoxic assay were used for detection of antisperm antibody. The change of levels of antisperm antibody before and after treatment, pregnant rate, and the number of implantation were investigated in tested mice.

RESULTS: The pregnant rates in normal saline group, prednisone group, Tai-bao high dose group and low dose were 38.89%, 47.06%, 70.00% and 75.00% respectively. The rate of pregnancy in Tai-bao low dose group was significantly higher as compared with normal saline group ($P < 0.05$). The rate of implantation in Tai-bao low dose group was significantly higher than that in prednisone group ($P < 0.05$). The results of detection of cytotoxic antibody to sperm showed that cytotoxic percentages in Tai-bao high dose group (63.0 +/- 10.3%) and prednisone group (56.3 +/- 13.7%) were significantly lower ($P < 0.05$ and $P < 0.01$) than that in normal saline group (72.84 +/- 5.05%).

CONCLUSION: Chinese medicine Tai-bao possesses regulatory effect on reproductive immune function, inhibitory effect on antisperm cytotoxic antibody, and promoting effect on pregnancy.

Lai AN; Song JF; Liu XJ Xiyuan Hospital, China Academy of TCM, Beijing.

Chung Kuo Chung Hsi I Chieh Ho Tsa Chih, 17(6):360-2 1997 Jun (ISSN: 1003-5370)

19. Clinical study on the treatment of male immune infertility by Huzhangdanshenyin

OBJECTIVE: To investigate the efficacy of the Chinese medicine Huzhangdanshenyin on male immune infertility, and provide an effective therapy for this disease. **METHODS:** Ninety men with immune infertility were selected as the research subjects and randomly divided into two groups, 60 in the treatment group, treated by Huzhangdanshenyin, and the other 30 in the control, treated by prednisone, both for 3 months. The improvement of clinical symptoms, immunologic indexes (antisperm antibodies in serum and seminal plasma) and sperm indexes (semen liquefied duration, motility, viability, density and abnormal morphology rate) were observed and the results analyzed. **RESULTS:** The total antisperm antibody reversing ratio of the treatment group was higher than that of the control ($P < 0.01$), especially the serum antisperm antibody reversing ratio. There were significant differences in the clinical cure rate and total validity rate between the treatment group and the control ($P < 0.01$). After the treatment, the markers of the clinical symptoms ($P < 0.01$), especially the serum antisperm antibody reversing ratio.

There were significant differences in the clinical cure rate and total validity rate between the treatment group and the control ($P < 0.01$). After the treatment, the markers of the clinical symptoms were lower ($P < 0.01$), and the improvement of the clinical symptoms was better in the treatment group than in the control ($P < 0.01$), especially the symptoms of pain in the back and knees, distending and bearing-down sensation of the perineum and testis, hypersexuality and topoalgia. Compared with pre-treatment, sperm motility and viability of the treatment group significantly improved ($P < 0.01$), and so did sperm density ($P < 0.05$). However, there were no significant differences in sperm density, semen liquefied duration, abnormal morphology rate and pH ($P > 0.05$) before and after the treatment.

CONCLUSION: The Chinese medicine Huzhangdanshenyin works more effectively than prednisone in the treatment of male immune infertility. It could improve the antisperm antibody reversing ratio, clinical symptoms and signs and ameliorate sperm indexes with no obvious adverse effects.

Lu TK, Ouyang HG, Jin GY, Hong YS, Zou Q, Lin ZY, Deng LS, Guo YB.
Zhonghua Nan Ke Xue. 2006 Aug;12(8):750-5.
Department of Andrology, Xiamen TCM Hospital Affiliated to Fujian TCM College,
Xiamen, Fujian 361001, China.

20. Direct effects of Chinese herbal medicine "hochuekkito" on sperm movement

BACKGROUND AND PURPOSE: Chinese herbal medicine, "Hochuekkito" is widely used for male infertility in Japan. There have been many reports concerning its clinical usefulness but very few reports of in vitro experiments studying the mechanism of its effects. In addition to stimulating germ cells, we analyzed its direct effects on sperm using computer assisted semen analyzer (CASA).

MATERIALS AND METHODS: Motile sperm were prepared using swim up technique from semen collected from ten healthy volunteers. Sperm movements (motility, velocity, linearity) were analyzed by CASA after adding either serum containing anti-sperm antibody (ASA) or normal serum with or without Hochuekkito.

RESULTS: Two hours after adding serum with ASA, the decrease of sperm motility was significantly reduced from 25.1% (92.8%→67.7%) to 12.5% (92.9%→80.6%) by adding Hochuekkito. No significant difference in velocity and linearity was observed between two groups. By adding normal serum, any of three parameters differed significantly with or without Hochuekkito.

CONCLUSION: Protective effects of Hochuekkito on sperm was suggested. Although normal sperm with ASA was used in this report, since the sperm of infertile patients are said to be more fragile, this results imply that direct protective effect is one of the mechanism of Hochuekkito for male infertility

Yamanaka M; Kitamura M; Kishikawa H; Tsuboniwa N; Koga M; Nishimura K; Tsujimura A; Takahara S; Matsumiya K; Okuyama A Department of Urology, Osaka University Medical School

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21. A substance isolated from *Cornus officinalis* enhances the motility of human sperm

The effects of a Chinese herb, *Cornus officinalis*, on the motility of human sperm was studied. An aqueous extract was prepared from the dried fruits of the herb and used in this study. The crude extract at a final concentration of 0.5 microgram/microliter in phosphate buffered saline (pH 7.4) increased sperm motility from 25.8 +/- 7.7% to 42.8 +/- 10.3% (i.e. 68% increase, n = 7), as determined by the computer-aided-sperm-analysis (CASA) method. The crude extract was fractionated by high-performance liquid chromatography (HPLC) into four fractions: C1, C2, C3 and C4. Their effects on sperm motility were further studied by CASA. Only the C4 fraction showed substantial stimulatory effects on sperm motility. At a concentration of 5 ng/microliter, C4 increased the sperm motility from 15.7 +/- 3.8% to 34.5 +/- 6.4% (i.e. 120% increase, n = 6) by CASA and from 14.9 +/- 4.3 to 28.5 +/- 8.1 (i.e. 91% increase, n = 8) by transmembrane migration ratio (TMMR) method. This result suggests that C4 is the active component in *Cornus officinalis* that enhances sperm motility.

Jeng H; Wu CM; Su SJ; Chang WC Department of Anatomy, Taipei Medical College, Taiwan.

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22. Plants Used in Chinese Medicine for the Treatment of Male Infertility Posses Antioxidant and Anti-Oestrogenic Activity

In this study Chinese herbs commonly used in the treatment of male infertility were investigated for relevant biochemical activity. Male factor infertility predominantly arises via barriers to, or defects in, spermatogenesis. The process of spermatogenesis is under strict endocrine control; in addition oxidative stress has been implicated in male infertility with significant levels of reactive oxygen species detected in 25% of infertile males. A total of 37 individual herbs and seven herb decoctions used in the treatment of male factor infertility were therefore tested for endocrine activity using a recombinant yeast based assay and antioxidant activity using the FRAP (ferric reducing antioxidant potential) assay. Individual herbs tested did not show androgenic properties, 20 showed strong and 10 weak anti-oestrogenic activity (per g of dried herb tamoxifen equivalents ranged from 1.18–1280.66mg and 0.06–0.98mg, respectively). Oestrogenic responses were elicited for two herbs (85.30–550µg oestradiol equivalents/g dried herb), with seven and three herbs exhibiting a strong or weak anti-androgenic response (per g of dried herb DHT equivalents ranged from 1.54–66.78mg and 0.17–0.32mg), respectively. Of these 37herbs, strong (15herbs), intermediate (7herbs) and weak/no (15herbs) antioxidant activity was detected (ranging from 0.912–1.26; 0.6–0.88 and 0–0.468µg ascorbate equivalent/mg dried herb, respectively). The seven decoctions (previously used to treat patients) tested elicited strong (5herbs) and weak (2herbs) anti-oestrogenic responses (per g of dried herb tamoxifen equivalents ranged from 1.14–13.23mg and 0.22–0.26mg, respectively), but not oestrogenic, androgenic nor anti-androgenic, consistent with their individual composition. With regard to antioxidant activity the following responses were recorded: three strong, three intermediate and one weak

(ranging from 1.02–1.2; 0.72–0.76 and 0.44 μ g ascorbate equivalent/mg dried herb, respectively). The prospects for introducing Chinese herbal treatments into the Western-based medicine are discussed.

Helen G. Tempest, Sheryl T. Homa, Edwin J. Routledge, Anthony Garner, Xiao-Ping Zhai and Darren K. Griffin. Systems Biology in Reproductive Medicine. 2008, Vol. 54, No. 4-5, Pages 185-195 (doi:10.1080/19396360802379073)

23. Intervention of different herbs on high serum leptin in women with polycystic ovary syndrome

Objective To investigate the effects of two prescriptions on patients with polycystic ovary syndrome (PCOS) patients. **Methods** In 43 PCOS women(PCOS group), 25 PCOS women diagnosed with SHEN-YIN deficiency syndrome were treated by nourishing yin for lowering fire recipe(nourishing yin group);18 PCOS women diagnosed with PI-QI deficiency syndrome were treated by strengthening the pi and replenishing qi recipe (benefiting qi group), 20 ovulatory controls was included as control group. Measurements of body mass index (BMI),waist-to-hip ratio(WHR), waist circumference (WC),fasting leptin,INS,T levels in women with PCOS and controls. **Results** Before treatment, BMI,WHR, WC and the serum leptin,INS,T levels of PCOS group,nourishing yin group and benefiting qi group were significantly higher than those of the controls (P0.01); After adjustment by BMI, WHR or WC, the differences in leptin,INS,T concentration between PCOS and controls were still statistically significant. Among of the 43 PCOS patients, 33 patients had elevated serum leptin, but the distribution of patients with elevated leptin level between the two syndromes had no significant difference (P0.05). After treatment, BMI, WHR and WC of PCOS group (nourishing yin group and benefiting qi group) had no significant changes, however, serum leptin, T and INS levels were lower than those before treatment (P0.05 to P0.01). After treated with nourishing yin, serum testosterone and insulin levels nourishing yin group decreased significantly(P0.05). After treated with strengthening pi and replenishing qi recipe, serum insulin levels in benefiting qi group decreased significantly(P0.01).Both 25 PCOS women with SHEN-YIN deficiency syndrome (nourishing yin group)and 18 PCOS women with PI-QI deficiency syndrome(benefiting qi group) had a decrease in serum leptin without statistical significance (P0.05); The total 43 of PCOS patients had a significant reduction of serum leptin level(P0.05). **Conclusions** TCM syndrome differentiation dependant therapy significantly lowered serum leptin concentration in PCOS women. Abnormal increase in serum leptin level in PCOS can not be ignored in the occurrence and development of this disorder, different herbs can lower serum leptin level, and can improve the state of high testosterone and high insulin in PCOS patients.

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