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Does dong quai have estrogenic effects in postmenopausal women? A double-blind, placebo-controlled trial

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Objective: To evaluate possible estrogenic effects of dong quai on vaginal cells and on endometrial thickness in postmenopausal women.
Design: Double-blind, randomized, placebo-controlled clinical trial.
Setting: Department of Obstetrics and Gynecology in a large health maintenance organization (HMO).
Patient(s): Seventy-one postmenopausal women (mean age [±SD], 52.4 ± 6 years) who had follicle-stimulating hormone levels (third-generation assay) of >30 mIU/mL with hot flashes.
Intervention(s): Subjects were randomized to treatment with either dong quai or placebo for 24 weeks.
Main Outcome Measure(s): Endometrial thickness was measured by transvaginal ultrasonography; vaginal cells were evaluated for cellular maturation; menopausal symptoms were evaluated by reviewing the Kupperman index and the diary of vasomotor flushes.
Result(s): We observed no statistically significant differences between groups in endometrial thickness, in vaginal maturation index, in number of vasomotor flushes, or in the Kupperman index.
Conclusion(s): Used alone, dong quai does not produce estrogen-like responses in endometrial thickness or in vaginal maturation and was no more helpful than placebo in relieving menopausal symptoms. (Fertil Steril® 1997;68:981–6. © 1997 by American Society for Reproductive Medicine.)

Key Words: Dong quai, alternative therapy, herbal therapy, climacteric

For many years, hormone replacement therapy (HRT) has been the standard treatment for menopausal symptoms. However, postmenopausal women may decide not to take HRT or to discontinue it because of concern about adverse events (1). This concern has led an increasing number of women to seek nontraditional or alternative remedies for menopausal symptoms. A recent survey indicated that 34% of U.S. adults used at least one alternative therapy within the previous year (2).

In a survey done in 1996 among women aged 45

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to 54 years who were members of the Kaiser Foundation Health Plan in Northern California, 5.5% of the women had used herbal remedies during the previous year and 10.8% had used herbal remedies at some time. For the past 3 years, sales of Rejuvex®, the most popular health remedy containing dong quai, have been extensive among hundreds of thousands of users in the United States.

In the Chinese Materia Medica, dong quai (danggui, tang-kuei) is indicated for disorders of menstruation including menopausal symptoms (3). The herb is extracted from the root of *Angelica sinensis* and is used in traditional Chinese medicine to strengthen the energy that emanates from the blood (3). The symptoms of "deficient blood energy" listed in Chinese texts are similar to those that Western medicine associates with menopause: menstrual flow abnormalities, nervousness, dizziness, insomnia, and forgetfulness.

Dong quai has been used in traditional Chinese medicine for >2000 years but has not been rigorously tested for safety and efficacy in standard clinical trials. Dong quai might enhance endogenous estrogen production, contain estrogenic substances, or alleviate symptoms of estrogen deficiency without altering estrogen levels. Whether dong quai contains phytoestrogens is unclear (4).

The primary purpose of this study was to test objectively for estrogenic effects of dong quai. In this double-blinded, placebo-controlled study, we considered tropic effects on the vaginal and endometrial linings as indicators of estrogen effect, and we also assessed dong quai's effects on menopausal hot flashes. We determined whether dong quai would alter endogenous production of estradiol or estrone.

MATERIALS AND METHODS

Subjects

Study participants were solicited through radio, television, and newspaper and magazine infomercials. The media campaign produced 886 phone calls. Preliminary telephone screening excluded 760 women for the following reasons: previous hysterectomy; serious illness; hormone therapy during the previous 3 months; use of herbal therapy during the previous month; weight >30% or <15% of ideal weight; gastrointestinal disorders that resulted in chronic diarrhea or malabsorption; history of breast cancer, pelvic irradiation, tobacco use, or consumption of more than two alcoholic drinks per day; active liver disease; chronic use of antibiotics; use of vaginal creams or corticosteroids; and inability or unwillingness to participate in a randomized clinical trial.

Of 116 screened women who qualified for the study, 25 refused further participation. The remaining 91 women were healthy and ambulatory, had been postmenopausal for at least 6 months, and had troublesome night sweats or vasomotor flushes (>14 combined events per week of any severity or >5 moderate to severe combined events per week). Of 91 subjects, 8 were subsequently excluded for the following reasons: level of follicle-stimulating hormone (according to a third-generation assay) of <30 mIU/mL ($n = 6$), decrease in number of vasomotor symptoms ($n = 1$), or chronic use of erythromycin ($n = 1$).

The results of mammography and Papanicolaou smears during the previous year were normal for all of the 83 women who were further screened. Seven women declined to participate at the initial visit, and five were excluded because their initial endometrial thickness exceeded 5 mm. The remaining 71 women were randomized to treatment using either dong quai or placebo.

The study protocol was approved by the Institutional Review Board at the Kaiser Permanente Medical Care Program in Northern California. A description of the study, its risks, and its benefits was provided to all participants who gave written informed consent. All patients who had been taking vitamins at the initial visit agreed to continue at the same dosage throughout the study.

Preparation of Dong Quai and Placebo

Dong quai was extracted from the crushed root of *Angelica sinensis* by East Earth Herbs, Inc (Eugene, OR). An aqueous extract was air-dried to yield a granular powder. This powder was mixed with the marc (residual root material) so that the weight of the finished product was similar to that of the initial root material (i.e., 1 g of finished product represented 1 g of root material). The potency of the study drug material was standardized to 0.5 mg/kg of ferulic acid by using high-performance liquid chromatography (HPLC) as the method of quantitation.

Maltodextrin was used as placebo. Oil of orange was added to all study drug material (active dong quai and placebo) to disguise the aroma of the dong quai. Dong quai and placebo were both dispensed in identical opaque capsules.

Drug Assignment

Participants were assigned randomly in blocks of four to either dong quai or placebo groups by using computer-generated random numbers. Subjects were instructed to take three capsules three times daily, equivalent to taking 4.5 g of dong quai root daily.

Clinic Visits

After the initial visit, subjects returned for clinical assessment at 6, 12, and 24 weeks. Study drug material was counted at all visits, and percentage compliance was calculated. Serum estrogen levels and vaginal cells were evaluated at the initial visit and at 12 weeks. Blood pressure and weight were measured at the initial, 12-week, and 24-week clinic visits. Endometrial ultrasonography was done at all visits. Women in whom transvaginal ultrasonography showed >5 mm endometrial thickness at the final visit (i.e., at 25–26 weeks) were evaluated by using endometrial biopsy to exclude the possibility of endometrial abnormalities. Biopsies were done with use of a Pipelle™ suction curette (Unimar, Wilton, CT).

Transvaginal Ultrasonographic Evaluation

Double endometrial thickness as viewed longitudinally was determined by using transvaginal ultrasonography at all visits. We used an Acuson 128XP™ ultrasonography machine (Acuson, Mountain View, CA) equipped with a 5-MHz endovaginal transducer (model EV 519). A tissue-mimicking phantom (model 412, Radiation Measurement Inc, Middleton, WI) was used to calibrate the instrument. Measurement error was ±3% as determined by using the 0.5-mm phantom.

Vaginal Cytology

Cytologic examination of vaginal smears was performed twice, i.e., once at the initial visit and again after 12 weeks of study. Vaginal smears were taken from the upper third of the left and right vaginal walls by using a wooden spatula and were immediately spray-fixed. These slides were then stained by the method of Papanicolaou (5). One technician, who was masked to the subject's treatment, determined the percentage of parabasal, intermediate, and superficial cells (6) for each slide by counting 100 cells. Slides were not analyzed if they were unsatisfactory (9.5%); if they showed inflammation, cytolysis, or distorted cell architecture; or if they contained an insufficient number of cells. The Maturation Value (7) was calculated as the sum of superficial cell percentage ×1 and intermediate-cell percentage ×0.5.

Menopausal Symptoms

Throughout the study, each subject kept a diary recording the total number of vasomotor episodes each day. At each clinic visit, we assessed each subject's score on the Kupperman index (8), a weighted index based on 11 symptoms of menopause: vasomotor symptoms, paresthesia, insomnia, nervousness, melancholia, vertigo, fatigue, arthralgia/myalgia, headache, palpitation, and formication. Scores ranged from 0–3 and indicated no symptoms (score = 0), mild complaints (score = 1), moderate complaints (score = 2), or severe complaints (score = 3). To calculate the Kupperman index, symptoms were weighted as follows: vasomotor symptoms, ×4; paresthesias, ×2; insomnia, ×2; and nervousness, ×2.

Laboratory Tests

Immunoassays for determining levels of serum estradiol, estrone, and sex hormone-binding globulin (SHBG) were done at Endocrine Sciences Laboratory (Calabasas Hills, CA).

Statistics

Student's t-test and χ^2 test were used to evaluate the statistical significance of the difference between dong quai and placebo groups in initial characteristics and in changes in outcome during the study. The study was designed to have ≥90% power to detect the following differences between groups: 2 mm in endometrial thickness; 7 points in Kupperman index; and 11 vasomotor episodes each week.

RESULTS

Table 1 shows values for baseline variables among women in the dong quai and placebo groups. Randomization was successful; groups showed no statis-

Table 1 Initial Characteristics of 71 Women Treated With Dong Quai or Placebo for Menopausal Symptoms

Characteristic	Treatment group	
	Placebo (n = 36)	Dong quai (n = 35)
Mean age (±SD) in years	52.6 (±6.0)	52.2 (±4.0)
Mean body mass index (±SD) (kg/m^2)	23.8 (±4.9)	25.0 (±3.3)
Mean no. of years (±SD) of education	15.3 (±2.3)	15.9 (±3.1)
Mean (±SD) age at menarche	12.7 (±1.7)	12.9 (±1.6)
Mean (±SD) no. of years since menopause	4.3 (±4.2)	3.1 (±2.2)
Range	0.5–20.3	0.6–9.3
Race (%)		
White	63.9	74.3
African American	19.4	11.4
Hispanic	2.8	5.7
Asian	11.1	5.7
Ever used hormone replacement therapy (%)	44.4	40.0
Ever used herbal remedies (%)	22.2	25.7
No. of alcoholic drinks per day (%)		
None	41.7	22.9
<1	52.8	62.9
1–2	5.5	14.2
Regular exercise (%)	57.1	57.1
Sexually active (%)	50.0	57.1

Note: The differences between the placebo and dong quai were not statistically significant.

tically significant differences. Ages ranged from 44.7–69.3 years in the placebo group and from 44.5 to 59.6 years in the dong quai group. Participants generally had a high level of education, and about one in four subjects had used herbal remedies previously.

Among women receiving placebo, six (16.6%) dropped out of the study; these included two women who dropped out because of lack of efficacy, two in whom minor side effects developed, one who lost interest, and one woman in whom other health problems developed. Among women receiving dong quai, four (11.4%) dropped out of the study; these included two women who dropped out because of lack of efficacy, one in whom minor side effects developed, and one woman in whom other health problems developed.

Compliance with study protocol was excellent: >75% compliance was achieved by 78.8% of women receiving dong quai and by 83.3% of women receiving placebo. Participants were unable to distinguish between active drug and placebo; 45.7% of subjects receiving placebo and 47.1% of subjects receiving dong quai believed they were taking the active drug.

Both treatment groups noted similar side effects during the study. Dong quai and placebo groups most frequently reported burping (22.9% versus 31.4%), gas (22.9% versus 25.0%), and headache (14.3 versus 16.7%).

Table 2 summarizes outcomes over time. An individual mean increase of 0.8 mm (for dong quai group) and 2.3 mm (for placebo group) in endometrial thickness was seen during the 24 weeks of the study, but no statistically significant differences in endometrial thickness were seen between placebo and dong quai groups. Of four women who had a menstrual period with typical changes in endometrial thickness, three had received placebo and one had received dong quai.

At the 24-week visit, 12 women had endometrial thickness of >5 mm: 3 had received dong quai and 9 had received placebo. Endometrial biopsies done in these subjects showed cellular changes ranging from atrophy to disordered proliferation. A progestin challenge test administered to 8 of these 12 women produced bleeding in 5 women, 1 of whom had received dong quai and 4 of whom had received placebo.

At the initial visit, most subjects (77.8% of the placebo group and 71.4% of the dong quai group) had a vaginal cytology pattern that showed dominance of intermediate cells, indicating that few women had an atrophic pattern. The cytologic pattern did not change between the initial and 12-week assessments. No statistically significant increase was seen

Table 2 Outcomes of Treatment With Dong Quai or Placebo for Menopausal Symptoms

Outcome	Baseline	6 weeks	12 weeks	24 weeks
Kupperman index				
Placebo	21.8 (7.5)	14.2 (6.4)*	15.0 (6.2)*	15.2 (8.9)*
Dong quai	19.0 (8.4)	11.3 (7.2)*	12.6 (6.6)*	12.2 (5.2)*
Vasomotor episodes (/wk)				
Placebo	33.2 (26.4)	33.8 (28.5)	29.3 (26.2)	26.9 (28.8)
Dong quai	47.3 (39.9)	35.4 (21.3)	34.9 (23.3)	30.7 (21.7)
Endometrial thickness (mm)				
Placebo	2.5 (0.7)	3.0 (0.7)*	3.6 (2.3)†	4.7 (2.4)*
Dong quai	2.6 (1.1)	3.0 (2.0)	3.4 (2.0)	3.5 (2.2)‡
Maturation value				
Placebo	40.7 (24.2)		38.7 (22.9)	
Dong quai	38.1 (26.1)		38.1 (26.6)	
Percent superficial cells				
Placebo	8.1 (10.9)		6.4 (11.6)	
Dong quai	8.0 (15.7)		9.5 (20.8)	
Serum estradiol (pg/mL)§				
Placebo	9.0 (11.8)		8.8 (10.3)	
Dong quai	11.8 (17.1)		8.9 (11.8)	
Serum estrone (pg/mL)				
Placebo	20.7 (9.8)		23.1 (16.3)	
Dong quai	23.0 (14.7)		20.9 (8.1)	
SHBG (μg/dL)§				
Placebo	1.76 (.71)		1.67 (.70)	
Dong quai	1.77 (.81)		1.71 (.83)	
Vaginal dryness (moderate/severe)‖				
Placebo	33.3		29.3	
Dong quai	45.4		29.0	

Note: SHBG = sex hormone-binding globulin.
* $P < 0.001$ (versus initial values).
† $P < 0.01$ (versus initial values).
‡ $P < 0.05$ (versus initial values).
§ Group mean (±SD).
‖ Percentage of subjects.

in the percentage of superficial cells or in the Maturation Value at 12 weeks in either the dong quai group or in the control group. The average Maturation Value for both groups at 12 weeks was <40, a result consistent with a menopausal, nonestrogenic pattern (9).

During the study, the Kupperman index and number of vasomotor episodes were reduced by about 25%–30% from initial values, and no statistically significant differences were seen between treatment with active drug and treatment with placebo. Subjectively, few women (29.4% of the placebo group and 33.3% of the dong quai group) reported good or excellent control of their vasomotor symptoms. At the initial visit, about 40% of subjects complained of moderate to severe vaginal dryness; 12 weeks later, about 30% still had this symptom.

No statistically significant changes in serum estradiol level, estrone level, SHBG level, blood pressure, or weight were seen during the study.

DISCUSSION

We found no differences in menopausal outcomes between the dong quai and placebo groups. Our methods were rigorous and had sufficient power to detect relatively small differences; for example, we could have detected a 30% reduction from initial Kupperman index scores or in number of vasomotor episodes or a doubling in basal endometrial thickness. To avoid spurious factors that could have influenced menopausal symptoms, we chose participants who did not smoke, use alcohol excessively, or have extreme variations in weight.

In a 24-week study (10), estrogen was shown to rapidly and progressively increase endometrial thickness. The mean weekly increase for women receiving full-strength estrogen therapy (e.g., 0.625 mg of conjugated estrogen) was 0.19 mm; it was 0.08 mm for those taking half this dose. In the present study, endometrial thickness increased at a mean rate of 0.06 mm/wk. This increase may have resulted from endogenous estrogen production because many participants had recently become menopausal. However, no statistically significant association was seen between endometrial growth and number of years since menopause. Moreover, excluding the four women who had a menstrual period, the study did not yield a different mean rate of endometrial growth.

Dong quai did not promote endometrial proliferation; the mean increase in endometrial thickness tended to be greater among women receiving placebo than among women receiving dong quai, even after adjusting for number of years since menopause. Of the biopsy specimens taken from three women receiving dong quai who had an endometrial thickness of >5 mm, none showed excessive cell proliferation or hyperplasia.

Studies investigating vaginal cytology in postmenopausal women have reported a wide range of maturation values. Baird et al. (11) reported an average of 15, whereas Utian (12) reported an average value of 46, a value similar to our findings. The small proportion of women in our study who showed atrophic maturation indices is probably attributable to our selection of subjects with vasomotor symptoms who tended to be recently postmenopausal. The low number of superficial cells counted in our study was similar to results reported from other researchers (13). Typically, estrogen therapy increases the percentage of superficial cells from 15%–30% (13) and the maturation value to >60 (14).

Effective treatment such as estrogen therapy is associated with a 60%–100% reduction in number of vasomotor episodes or in Kupperman index scores (15, 16). Placebo treatment is typically associated with 15%–25% reductions (17, 18). Our results thus appear to indicate a placebo effect. We expected to attract women who would be more receptive to alternative therapy, and almost 25% of participants had used herbal therapy in the past. Despite their possible enthusiasm for this type of treatment, few women were satisfied with its efficacy for relieving vasomotor symptoms. This result contrasted markedly with the widely recognized efficacy of estrogen therapy for relieving menopausal symptoms.

Use of dong quai alone can be criticized because traditional Chinese practitioners never prescribe dong quai alone. Typically, it is used in conjunction with four or more other herbs. An herbal mixture, *Angelica paeonia* powder (*Radix angelicae sinensis, Radix paeoniae lactiflorae, Rhizoma ligustici, Rhizoma atractylodes, Rhizoma alismatis, Sclerotium poriae*), has been reported to reduce menopausal disturbances, including vasomotor symptoms, by 70% (3). We tested dong quai alone because most women in the United States who take it to relieve menopausal symptoms purchase it in over-the-counter form as a single entity.

We conclude that when dong quai is used alone it is no more helpful than placebo in relieving menopausal symptoms. Dong quai does not produce discernible estrogen-like responses in vaginal cells or in endometrial thickness. Women should be discouraged from using this remedy alone to relieve menopausal complaints.

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