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Original article

The effect of curculigoside on mouse model of perimenopausal depression

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ABSTRACT

Objective: To investigate the effect of curculigoside on mice with simulated perimenopausal depression.
Method: Gavage with high, medium, small dose of curculigoside once daily for 30 d consecutive days. Record the related behavior index. The wet weights and viscera indexes of the mouse uterus, thymus, and spleen were measured. Half of the brain was homogenized and tested for 5-HT and DA concentrations. The levels of serum E2, T, FSH, and LH were measured as well. Finally, histological changes in the uterus, thymus, spleen, and hypothalamus were observed under a light microscope.
Result: curculigoside can enhance the activity and latency time of the mice, increase mouse memory, and decrease electric shocks and immobility times in the TST and FST experiments. Mice treated with curculigoside showed significantly enhancement in viscera indexes of the thymus, spleen, and uterus; significantly elevated levels of serum E2 and T; significantly increased brain 5-HT and DA concentrations; significantly decreased levels of serum FSH and LH; and improvements in the histopathological lesions of the uterus, hypothalamus, thymus, and spleen. The high dose of curculigoside produced the best results.
Conclusion: All doses of curculigoside are associated with reversing hormone (E2, T, FSH, and LH) disorders in perimenopausal syndrome and adjusting imbalanced 5-HT and DA levels, representing a therapeutic effect in perimenopausal depression.

1. Introduction

Perimenopausal depression is a mood disorder that occurs shortly before or after menopause in women aged 56 to 66. The main symptoms of perimenopausal depression include emotional depression, anxiety and stress (Xu et al., 2015), accompanied by endocrine dysfunction, especially hypogonadism and senescence (Li and Tian, 2012).

As a commonly-used medicine to tonify yang, curculiginis can enhance kidney yang, strengthen bones and muscles, and alleviate coldness and wetness in the body. Curculigoside content is one of the quality indicators for curculiginis herbs, which have the pharmacological effects of promoting gonadal function, enhancing immunity, anti-cancer and anti-aging (Huo et al., 2012). Clinically curculiginis is used in the treatment of impotence, menopause syndrome, benign prostatic hyperplasia, and breast hyperplasia. Here, we report our findings about the effect of curculiginis on perimenopausal depression.

2. Experimental materials

2.1. Experimental animals

Kunming female mice with masses of 18–22 g, were obtained from Henan Experimental Animal Center, with a batch certificate conformity number of 0008495. The Laboratory Certificate of Conformity is SYXK (Henan) 2010-001.

2.2. Experimental reagents

Curculigoside was obtained from Nanjing Zelang Medical Technology Co., Ltd., with a lot number of ZI20120824 and curculigoside content of 52.3%. Gengnian'an Capsules were obtained from Shanxi Star Pharmaceutical Co., Ltd., with a batch number of 120303 and an approval number of Zhun Z14021848. Soy isoflavones Vitamin E Soft Capsules were obtained from Weihai

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Unisplendour Biotechnolog Co., Ltd., with an approval number of Jian G20080032 and a batch number of 12040301.

Chloral hydrate was obtained from Tianjin Kermel Chemical Reagents Development Center with a lot number of 20120606. Sodium carboxymethyl cellulose was obtained from Tianjin Hengxing Chemical Reagent Co., Ltd., with lot number of 20110728. Penicillin G sodium (four million IU) for injection was obtained from North China Pharmaceutical Co., Ltd., with a lot number of c1107702. Formaldehyde solution (AR) was obtained from Yantai Shuangshuang Chemical Co., Ltd., with a lot number of 20120701. Mouse E2 ELISA kits were obtained from R&D with a lot number of 20121101A. Mouse T ELISA kits were obtained from R&D with a lot number of 20121101A. Mouse LH ELISA kits were obtained from R&D with a lot number of 20121101A. Mouse FSH ELISA kits were obtained from R&D with a lot number of 20121101A. Mouse 5-HT ELISA kits were obtained from R&D with a lot number of 20121101A. Mouse DA ELISA kits were obtained from R&D with a lot number of 20121101A.

2.3. Instrument

An electronic scale model JY601 was obtained from Shanghai Minqiao Medical Appliance Co., Ltd. An electronic analytical scale model AR1140/C was obtained from Ohaus Instruments (Shanghai) Co., Ltd. A high-speed desktop centrifuge model TGL-168 was obtained from Shanghai Anting Scientific Instrument Factory. An actophotometer model ZZ-6 was obtained from Chengdu Thaimeng Technology Co., Ltd. A passive avoidance apparatus model BA-200 was obtained from Chengdu Thaimeng Technology Co., Ltd. An electric heated thermostatic water bath model HWS12 was obtained from Shanghai Yiheng Scientific Instrument Co., Ltd. Adjustable pipettes were obtained from Shanghai Leibo Analytical Instruments Co., Ltd. A microplate reader model 680 was obtained from BIO-RAD (US). A motorized microscope (model BX61) was obtained from Olympus (Japan).

3. Method

3.1. Modeling and administration

Modeling method. We randomly chose twelve mice from among 100 female Kunming mice with masses of 22–25 g to use as a control group that received a sham surgery treatment. The remaining mice were used for a perimenopause model.

Each mouse was anesthetized by an intraperitoneal injection of 10% chloral hydrate after weighing (0.03 mL/10 g) and received an abdominal bit fix. Then the mouse was sheared from the back of the last rib in the axillary line at about 1 cm lateral distance from the spine. After disinfection, the skin and back muscles were incised about 0.5–1 cm. A milky-white, shiny, visible section of cellulite was exposed, in which the ovary is embedded. First, the ovarian tube including cellulite was clipped with a thin ligature, and then the ovary was removed. The uterine horns were replaced in the abdominal cavity. Finally, the muscles and skin were sutured. The same treatment was applied to both ovaries. Each mouse received three daily intramuscular injections of 200 ku/kg (0.1 mL/mouse) penicillin to prevent infection. Starting on the fifth day after surgery, a vaginal smear was applied to each mouse daily for five consecutive days to verify the complete removal of the ovaries. Mice with estrus reactions shown by the smear result were discarded. Sixty completely castrated mice were selected and randomly assigned into six groups, including a model group, Gengnian'an group, soy isoflavones group, and curculigoside groups receiving high, medium, and small dose. Ten out of the twelve mice from the previous control group were randomly chosen to continue in the control group.

After five days of administration, the control group continued receiving normal food and water with five mice per cage, while the six test groups began randomly receiving different stresses every day, with one mouse per cage. Seven stress factors were applied randomly for eighteen consecutive days, with one stress a day and no identical stress for two consecutive days. The stress factors comprised: 1. wet litter (g litter, mL water), 2. ice swimming (4 °C, five minutes), 3. heat stress (45 °C, five minutes), 4. night lights (24 h), 5. tail clamping (one minute), 6. water deprivation (24 h), and 7. fasting (24 h).

Method of administration. All groups began to receive their corresponding medication on day ten after surgery. The concentration of the Gengnian'an suspension was 675 mg/kg. The concentration of the soy isoflavones suspension was 250 mg/kg. The concentrations of curculigoside with high, medium, and small dose were 400 mg/kg, 200 mg/kg, and 100 mg/kg, respectively. The control group and model group received distilled water instead. The dosing volume was 0.1 mL/10 g, and each mouse received gavage once daily for thirty consecutive days.

2.2. Test items and method

Each mouse's spontaneous locomotor activities were measured for five minutes on the twenty-sixth day of administration. On the twenty-seventh day of administration, the latency time to enter the dark room as well as the number of electric shocks received by the mouse over five minutes due to entering the dark room were recorded to assess passive avoidance. The total immobility time from the second to sixth minute of the FST was recorded on the twenty-eighth day of administration. The total immobility time from the second to sixth minute of the TST was recorded on the twenty-ninth day of administration. Two hours after the last administration, which involved 12 h of fasting with water provided, each mouse was weighed and blood was collected via an eyeball removal procedure. The serum was separated and tested for estradiol (E2), testosterone (T), luteinizing hormone (LH), and follicle-stimulating hormone (FSH) concentrations using ELISA kits. Finally, each mouse was sacrificed by cervical dislocation and anatomized. The thymus, spleen, and uterus were extracted and wet weighed, and the viscera index was calculated (viscera index = viscera wet weight (mg)/mouse weight (g)). The brain was also extracted, and half of it was homogenized and measured for concentrations of monoamine neurotransmitter 5-hydroxytryptamine (5-HT) and dopamine (DA) using corresponding kits. The thymus, spleen, uterus, and remaining brain tissue were fixed in a 10% formaldehyde solution, embedded in paraffin, sectioned, and hematoxylin and eosin stain (HE) stained. Furthermore, the histological changes were observed under a light microscope.

2.3. Statistical methods

Data was analyzed using the SPSS17.0 statistical package. Quantitative data was represented by mean ± standard deviation (±s). ANOVA was used to compare among groups; least significant difference test (LSD) was used for data with homogenous variance, and Games-Howell was used for non-homogenous variance. Ordinal data was tested using the Ridit analysis.

3. Result

3.1. Effect on spontaneous locomotor activity of perimenopausal depression modeling mice

The test results for spontaneous locomotor activity for the different groups of mice are shown in Table 1.