

Effect of the Combination of Native Herb with Motherwort on Anti-Inflammatory, Anti-Fatigue, and Hypertensive Hypoxia Tolerance

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Abstract

Objective: To investigate the in vivo anti-inflammatory, anti-fatigue, and hypertensive hypoxia tolerance effects of earth ginseng with motherwort and its combination on mice. <u>Methods</u>: Male mice were divided into 6 groups according to their body weight: blank control group, native ginseng group, motherwort group, and three experimental groups with a 1:1 ratio of native ginseng and motherwort. 1.5, 4.5, and 7.5 g-kg-1 -d-1 were given to the three experimental groups. The blank control group was instilled with saline, and the earth ginseng group and motherwort group were given 1.5 g-kg -d-1-1 of the corresponding extracts. After 21 d of continuous gavage, the ear swelling test by xylene, the weight swimming test, and the high-pressure hypoxia tolerance test were performed. Also, the experimental indexes were measured, the liver weight was weighed, and the liver weight coefficient was calculated. <u>Results</u>: In the anti-inflammatory experiment, there was a significant difference in the swelling inhibition effect between the two single-flavored groups compared with the control group, the low-dose group compared with the two single-flavored groups, and the medium- and high-dose groups compared with the low-dose group (P < 0.05). In the weight swimming experiment and high-pressure hypoxia tolerance experiment, compared with the control group, the mice in the earth ginseng group and the motherwort group showed a significant improvement in weight swimming time and high-pressure hypoxia tolerance time ($P \le 0.05$); compared with the two single herb groups, the mice in the low dose group showed a statistically significant improvement in weight swimming time and high-pressure hypoxia tolerance time ($P \le 0.05$); compared with the low dose group, the mice in the high dose group showed a statistically significant improvement in weight swimming time and high-pressure hypoxia tolerance time ($P \le 0.05$). Compared with the low-dose group, the high-dose group had a statistically significant (P < 0.05) improvement in weight-bearing swimming time and

hyperbaric hypoxia tolerance time. Compared with the control group, the liver weight coefficient of the earth ginseng group was statistically significant (P < 0.05); compared with the two single herb groups, the liver weight coefficient of the low-dose group was statistically significant (P < 0.05); compared with the low-dose group, the liver weight coefficient of the middle and high-dose groups were statistically significant (P < 0.05). *Conclusion*: Native herbal medicine and its combination have significant anti-inflammatory, anti-fatigue, and high-pressure hypoxia tolerance effects, and the anti-inflammatory effect was positively correlated with the increase of the extract concentration; the anti-fatigue and high-pressure hypoxia tolerance effects were the best in the high-dose group.

Keywords: native ginseng, motherwort, combination, anti-inflammatory, anti-fatigue, hypoxia tolerance, high pressure

1. Introduction

Native ginseng (Talinum paniculatum) is a perennial herb with a sweet taste and flat nature. It is used for treating qi deficiency, spleen deficiency, lung dryness, and scanty lactation; it has various effects such as benefiting qi and moistening the lung (Lu LF, Lin MY, Huang SY, et al., 2018). Motherwort (Leonurus japonicas Houtt.) is bitter, pungent, and slightly cold in nature, and is a member of the Labiatae family. It has the effects of regulating menstruation, diuretics, and clearing heat and detoxification. Studies have shown that motherwort not only has low toxicity and high safety but can also myocardial ischemia improve and microcirculation, protect the kidneys, be antithrombotic and anti-inflammatory, and analgesic. It is widely used in the treatment of gynecological diseases, such as incomplete abortion and menstrual insufficiency (Ye LH, He M, Zhao XQ, et al., 2019; Wei XX, Di S, Guo HX, et al., 2020; Li Yun-Yun, Lin Yi-Kong, Liu Xin-Hua, et al., 2020). Studies have shown that motherwort bases can improve striatal neuron damage in brain ischemia (Wang J, Wang SJ, Li J, et al., 2019). Eriocitrin feedback inhibits the expression of Apelin and APJ to improve the hypoxic-ischemic injury of immature myocardium (Zhang LN, Wu XH, Wang P, et al., 2018).

Both Ginseng and Motherwort are known to contain polysaccharides and flavonoids that have been proven to have antioxidant effects and therapeutic benefits against various diseases. Additionally, several studies have demonstrated that these two herbs possess a range of pharmacological effects and other chemical components.

To date, there have been no domestic or foreign

reports on the combined effects of Earth Ginseng and Motherwort. However, it is worth noting that divers who work in high-pressure environments face difficulties in breathing and may experience adverse effects on their physical and mental health.

The high-pressure hypoxia tolerance effect observed in this study differs from previous hypoxia tolerance experiments. Furthermore, the medicinal value of Motherwort and Earth Ginseng will continue to be explored, providing new research ideas for the development of anti-inflammatory and anti-fatigue high-pressure hypoxia tolerance drugs in clinical settings.

2. Materials and Methods

2.1 Materials

2.1.1 Animals

SPF grade Kunming breed mice, all male, weight (20±2) g, week age unknown. Provided by the Experimental Animal Center of the Right River School of Ethnic Medicine, Baise, Guangxi, China, License No.: SCXK Gui 2012-0003.

2.1.2 Instruments and Consumables

Rotary evaporator: circulating water vacuum multi-purpose pump shock-resistant pressure gauge; helium cylinder; FA1204B electronic balance; JSC electronic Balance Scale CN-BH; TH-UP-10 laboratory special ultra-pure water machine; clean grade experimental rat maintenance feed.

2.1.3 Drugs

The Chinese herbal medicines Tulip Ginseng and Yimoucao were identified by Professor Huang Lockyi, Director of the Scientific Experiment Center of the Right River College of Ethnic Medicine and confirmed to be the dried stems of Tulip Ginseng Talinum paniculatum of the family Amaranthaceae and the dried stems and leaves of Yimoucao Leonurus japonicas Houtt. of the family Labiatae.

2.2 Methodology

2.2.1 Animal Grouping and Drug Administration

After one week of acclimatization feeding, a total of seventy-two male Kunming breed mice of SPF grade were weighed and randomly assigned to six experimental groups based on their body weight. Each mouse was labeled with 5% picric acid. The experimental groups included a blank control group, an Earth Ginseng group, a Motherwort group, a low-dose group, a medium-dose group, and a high-dose group.

The blank control group was given an equal volume of 0.9% saline via gavage. The two mono-dose groups were given the corresponding Chinese herbal extracts at a body mass of 20 mL-kg⁻¹ via gavage. The three dose groups were given three different concentrations of 1.5, 4.5, and 7.5 g-kg⁻¹ -d⁻¹ at a body mass of 20 mL-kg⁻¹ via gavage once every 24 hours for 21 consecutive days. The body mass of the mice was measured every three days during the experiment to ensure the accuracy of the gavage dose and maintain experimental rigor. Ethical requirements for animal experiments were strictly observed throughout the study.

2.2.2 Drug Extraction

Referring to the method (Yi ZX & Yang L., 2016), the extract was prepared by weighing 100g of root and leaf mixture, adding 10 times the volume of distilled water, soaking for 30 minutes, then decocting for 30 minutes, filtering and removing the residue as I liquid; then adding 8 times the volume of water, decocting for 15 minutes, filtering as II liquid; mixing I and II liquid, concentrating to 100% under reduced pressure, i.e., the concentration of ginseng liquid is 1 g/mL, and refrigerating.

Take 400 g of motherwort herbs and add distilled water in the ratio of 1:10, soak for 4 h, then decoct twice for 1 h each time, filter each time through multiple layers of gauze and then combine the filtrate obtained twice, concentrate under reduced pressure to 100%, refrigerate at 4°C and set aside.

The low, medium, and high dose groups were prepared in three concentrations of 1.5, 4.5, and

7.5 g-kg-1-d-1 with a 1:1 concentration ratio of earth ginseng and motherwort, respectively.

2.2.3 Anti-Inflammatory Experiment of Ear Swelling in Mice Caused by Xylene

A total of seventy-two male SPF grade mice were grouped, administered, and gavaged according to the method outlined in section 1.2.1. The mice were gavaged for 21 days. On the 21st day, after 30 minutes of gavage, 0.04 ml of xylene was applied to both sides of the left ear to induce inflammation, while the right ear was left untreated.

After 30 minutes, the mice were euthanized by cervical dislocation, and the ear pieces were removed by punching holes in the same part of both ears using a 3 mm diameter puncher. The weight difference between the left and right earpieces was used to indicate the degree of swelling, and the swelling inhibition rate was calculated as follows: Swelling inhibition rate (%) = (mean value of model group - mean value of drug administration group)/mean value of model group × 100%.

2.2.4 Weight-Bearing Swimming Experiment in Mice

A total of seventy-two male mice of SPF grade were grouped, administered, and gavaged according to the method outlined in section 1.2.1. The mice were gavaged for 21 days. After the last gavage, the mice in each group were tied to a wire at the tail (7% of the mice's body weight) and placed in a plastic bucket with a water depth of 28 cm (more than the mice's tail length and body length). Two mice were placed in each bucket, and the water temperature was controlled at (30 ± 2) °C (Liang XJ, Lu M, Li ST, et al., 2017).

The mice were made to swim continuously, and the time was measured from the moment they entered the water to the time when they could not surface for 6 seconds, which was the time of exhaustion swimming. After recording the time, the mice were fished out.

2.2.5 Hypoxia Tolerance Test in Mice

To assemble the high-pressure device, a 100 ml plastic wide-mouth bottle was taken and plugged with a double-hole rubber stopper. The perimeter of the stopper was sealed with petroleum jelly. Two plastic tubes were inserted into the rubber stopper, with one tube connected to the helium bottle and the other tube connected to the shock-resistant pressure gauge. Seventy-two male mice of SPF grade were grouped, administered, and gavaged according to "1.2.1". The mice were gavaged for 21 days. On the 21st day, after 30 minutes of gavage, 100 ml plastic wide-mouth bottles were placed in the mice, and the mouths of the bottles were tightly covered with petroleum jelly to prevent air leakage. Assembly of the hyperbaric device was performed as described above.

After the hyperbaric experiment, the mice were dissected, and their livers were freed and weighed, and the liver weight of each mouse was recorded. The liver weight coefficient was calculated as follows: wet liver weight (g) / body weight (g) × 100% (Liang XJ, Huang XX, Lu M, et al., 2017).

2.2.6 Data Processing and Methodological Statistics

The data obtained from the experiment were expressed as mean \pm standard deviation ($x \pm s$), and statistical analysis was performed using the SPSS 17.0 software. The ANOVA t-test was used to compare the results between the two experimental groups, while the one-way

ANOVA method was applied to analyze the differences among multiple groups. The LSD and paired t-tests were utilized for inter-group comparison. The significance level was set at α =0.05.

3. Results

3.1 Anti-Inflammatory Effects of Native Ginseng and Motherwort and Their Combination on Xylene-Induced Ear Swelling in Mice

Based on the statement, it can be inferred that the experiment was conducted to evaluate the anti-inflammatory effects of earth ginseng and motherwort in a xylene-induced ear swelling model. The results suggest that the combination of earth ginseng and motherwort has a synergistic effect in inhibiting ear swelling. The low-dose group showed significant effects compared to the two single-medicine groups, and the middle and high-dose groups exhibited better effects than the low-dose group. The differences between the groups were statistically significant with a p-value less than 0.05. The details of the results are presented in Table 1.

Table 1. Effects of Radix Ginseng, Herba Leonuri and their combination on ear swelling induced by xylene in mice (`x±s, n = 12)

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Group	Left ear (mg)	Right ear (mg)	Left ear - right ear (mg)	Swelling inhibition rate (%)
Blank group	4.60±0.12	2.50±0.11	2.60±0.09	
Native Ginseng Group	3.70±0.08 ^a	2.20±0.14	2.80±0.15ª	19.57
Motherwort group	3.80±0.09 ^a	2.20±0.10	1.90±0.04 ^a	17.39
Low dose group	3.10 ± 0.08^{bc}	2.40±0.13	1.60±0.06	32.61
Medium dose group	2.70 ± 0.12^{d}	2.40±0.15	1.50 ± 0.12^{d}	41.30
High dose group	2.30±0.12 ^d	2.40±0.09	0.40 ± 0.03^{d}	50.00

Note: Compared with the blank control group, a) P < 0.05; compared with the earth ginseng group, b) P < 0.05; compared with the motherwort group, c) P < 0.05; compared with the low-dose group, d) P < 0.05

3.2 Effect of Earth Ginseng and Motherwort and Their Combination on Weight-Bearing Swimming Time in Mice

In the weight swimming experiment of mice, the weight swimming time of mice in the earth ginseng group and motherwort group was significantly (P < 0.05) improved compared with the blank group; the weight swimming time of

mice in the low-dose group was statistically significant (P < 0.05) compared with the two single-medicine groups; the high-dose group was statistically significant (P < 0.05) compared with the low-dose group, see Table 2 for details.

3.3 Effect of Earth Ginseng and Motherwort and Their Combination on Hypoxia Tolerance Time in Mice In the experiment of hypoxia tolerance in mice, the hypoxia tolerance time of mice in the earth ginseng group and motherwort group was improved significantly compared with the blank group (P < 0.05); the hypoxia tolerance time of mice in the low dose group was improved statistically compared with the two single flavor groups (P < 0.05); the hypoxia tolerance time of mice in the middle and high dose groups was improved compared with the low dose group, and the improvement effect of the high-dose

group was obvious (P \leq 0.05), see Table 2.

The liver weight coefficient of the earth ginseng group was statistically significant (P < 0.05) compared with the blank group; the liver weight coefficient of the low-dose group was statistically significant (P < 0.05) compared with the two single-medicine groups; The liver weight coefficients of the middle and high-dose groups were significantly higher (P < 0.05) compared with the low-dose group, as detailed in Table 2.

Table 2. Effects of Radix Ginseng, Herba Leonuri and their combination on weight-bearing swimmingtime and hypoxia tolerance time in mice (`x±s, n = 12)

Group	Weighted sv time (S)	wimming	High pressure hypoxia resistance time (S)	Liver coefficient (%)	weight
Blank group	51.51±1.46		341.06±4.71	4.9±0.4	
Native Ginseng Group	70.12 ± 1.75^{a}		415.63±14.22 ^a	4.5±0.03 ^a	
Motherwort group	70.42 ± 2.00^{a}		405.17±16.28 ^a	4.9±0.02	
Low dose group	81.97 ± 2.30^{bc}		445.83±14.01 ^{bc}	5.1 ± 0.01^{bc}	
Medium dose group	87.9±2.12		491.30±15.33	5.3 ± 0.03^{d}	
High dose group	124.36±5.24 ^d		597.7±18.17 ^d	6.1±0.09 ^d	

Note: compared with blank control group, a) P < 0.05; compared with Talinum paniculatum group, b) P < 0.05; compared with Leonurus japonicas Houtt. group, c) P < 0.05; compared with low-dose group, d) P < 0.05

4. Discussion

Inflammation is a primary pathological process underlying numerous diseases, characterized by local microvascular reactions and exudation of blood components (Shibo ZHAO, Suoyi HUANG, Xinpeng CHEN, et al., 2020). The severity of inflammation can be gauged by the levels of crucial inflammatory mediators such as PGE2, NO, and TNF- α (Shibo ZHAO, Suoyi HUANG, Zhenjing SI, et al., 2020). Given the complex chemical composition of herbal medicines, current trends in herbal analgesic medications aim to reduce adverse effects and minimize dependence (Zhao SB, Chen XY, Yu HL, et al., 2020).

Previous studies have demonstrated that the methanolic extract of Motherwort can effectively inhibit foot swelling in rats induced by carrageenan, and experimental evidence confirms that the flavonoid and polysaccharide components in Motherwort have antioxidant effects (Qiao JJ, Wu QN, Xue M, et al., 2018). All the polysaccharides present in native ginseng

possess scavenging effects on reactive oxygen radicals, enabling them to eliminate excess oxygen radicals generated in the body. Furthermore, high doses of earth ginseng leaves have been shown to effectively inhibit inflammatory exudation and granulation tissue formation (Wang X, Lin MY, Huang SY, et al., 2017).

The current experiment demonstrated that the combination of earth ginseng and motherwort in potent а 1:1 ratio exerted а more anti-inflammatory effect compared to single-drug administration. The results suggest that there is a synergistic effect between earth and motherwort in ginseng exerting anti-inflammatory effects. Additionally, the anti-inflammatory effect increased with an increase in the ratio concentration.

Fatigue is a multifaceted physiological process, with the primary cause being the inability of energy-supplying substances to meet the body's needs, leading to the accumulation of excessive metabolites in the body. Corresponding

enzymes in the body can maintain the production and removal of free radicals in a balanced state during the quiet state. An appropriate number of free radicals has significant physiological significance for the human body (Yu FR, Yang B, Li ZP, et al., 2017). The body can respond to different pressure exposures with a clear stress response, which is not synchronized with the pressure gradient. Within a certain range of physiological stress of high pressure, the stress level of an individual may exhibit a steady state (Sha AL, Hao HY., 2019). The effects of high-pressure gas on the organism are complex (Ma J, Feng L, Fang YQ, et al., 2019). In a hypoxic environment, appetite, digestion, and absorption are suppressed, reducing the energy intake required for the body's activities (Fu PY, Hu Y, Li YC, et al. 2019; Gong LJ, Fu PY, Zhu RX, et al., 2020). In chronic hypoxia, cells of the brain, heart, and other vital organs begin to die on a large scale by apoptosis due to the prolonged lack of energy supply. Additionally, many free radicals are produced in the body, leading to varying degrees of organ and tissue damage (Shi-Bo Zhao, Suo-Yi Huang, Yu-Xin Wei, et al., 2020).

Based on extensive research on anti-fatigue and hypoxia tolerance, this experiment adds the innovative element of high pressure. The data indicate that the combination of earth ginseng and motherwort has a more evident anti-fatigue and high-pressure hypoxia tolerance effect compared to the blank group and the single-herb group. Furthermore, there is a quantitative-effect relationship of a more significant effect with increasing ratio concentrations. Preliminarily, the reasons for the superior effect of the combination of the two drugs may be as follows: firstly, the liver weight coefficient increased with the increase of the proportional concentration. Considering that the combination of earth ginseng and motherwort could increase the liver glycogen reserve in mice, the liver glycogen reserve also increased with the increase of the proportional concentration of the two drugs, and the high-dose group exerted the most pronounced anti-fatigue effect. Secondly, in a high-pressure environment, the contraction and diastole of muscles are affected, with the contraction of respiratory muscles as the driving force of respiration and pulmonary elastic retraction force needing to counteract the external high pressure leading to pulmonary ventilation dysfunction. Considering that the

combination of earth ginseng and motherwort can continuously excite the muscle cells and produce greater contraction force. Thirdly, considering the hypoxia resistance effect of the combination of earth ginseng and motherwort and the synergistic effect of flavonoids and polysaccharides contained in both in scavenging reactive oxygen species and free radicals in the body.

In conclusion, this experiment has demonstrated that the combination of earth ginseng and motherwort has anti-inflammatory and anti-fatigue effects, as well as high-pressure hypoxia tolerance. The effect of the combination increased with the increase of the proportional concentration, with the best effect observed in the high dose group. However, this study is only a preliminary investigation, and further research is necessary to elucidate the mechanisms underlying the anti-inflammatory, anti-fatigue, and hyperbaric hypoxia tolerance effects of earth ginseng, motherwort, and their combination.

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