Original Article

A Novel Polyherbal Chicken Soup Improves Memory, Oxidative Stress and Cholinergic Function in Animal Model of Menopause

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Background: Despite the increasing importance of memory impairment in menopause, the current therapy against memory impairment in menopause is still limited. Therefore, the novel memory enhancer for menopause is required. Based on the crucial roles of oxidative stress and cholinergic function on memory and the synergistic concept, the memory enhancing effect of the polyherbal chicken soup which contains many herbs possessing antioxidant effect has gained attention. However, no supported evidence is available until now.

Objective: To assess the memory enhancing effect of the polyherbal chicken soup (WO1) and to determine the possible underlying mechanism in animal model of menopause.

Materials and Methods: Female Wistar rats were divided in to 6 groups: 1) sham plus vehicle, 2) OVX plus vehicle, 3) OVX plus isoflavone, 4 to 6) OVX plus WO1 at doses of 0.8, 1.6 and 2.4 $mg.kg^{-1}$ respectively. All rats were treated with the assigned substance for 35 days and memory assessment was performed every 7 days throughout the study period. Then, they were determined malondialdehyde (MDA) level together with the activities of superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and acetylcholinesterase (AChE) in hippocampus at the end of experiment.

Results: All doses of WO1 improved memory and decreased both AChE activity and MDA level in hippocampus of OVX rats. The enhanced SOD activity was observed in all WO1 treatment groups but the increased CAT and GPX activities were observed only in high dose treatment group.

Conclusion: WO1 can improve memory in experimental menopause. The mechanism may occur partly via the improvement of cholinergic function and oxidative status in hippocampus. Our data suggest that WO1 is the potential functional food targeting at memory enhancement for menopausal women. However, clinical study is still essential to confirm aforementioned health benefit.

Keywords: Polyherbal chicken soup, Memory enhancing effect, Oxidative stress, Ovariectomized rat

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Most menopausal women have the experience of memory impairment. It has been reported that the memory impairment rate in menopausal women is approximately 62 to 67%[1,2]. This impairment includes a difficulty in recalling words or numbers, forgetting events and actions, and a difficulty in concentrating. It has been reported that the memory impairment disturbs a daily life activity giving rise to a poor quality of life. However, this condition can be treated with estrogen therapy[3]. Unfortunately, this therapy is reported to increase the risks of breast cancer, heart disease and stroke[4]. Due to these adverse effects of hormone therapy, the demand for less invasive treatments to reduce and protect against menopause-related conditions is growing.

Accumulative lines of evidence have demonstrated that the decreased estrogen levels during menopause is associated with the enhanced oxidative stress[5-7] which occurs as the result of the imbalance between the formation of the reactive oxygen species and the buffering capacity of antioxidant system[8]. It has been reported that dietary supplements which are rich in antioxidants can protect against oxidative stress related memory impairment[9-16]. Based on these pieces of information, the beneficial effect of polyherbal chicken soup which is rich in substances possessing antioxidant activity on memory impairment induced by menopause has gained attention.

Since the memory impairment in menopausal women is increased its importance in accompany with the increased elderly population, many animal models of

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menopause have been developed. Bilateral ovariectomy is regarded as one of the validated animal model of menopause which can induce memory impairment following ovarian hormone deprivation[17-19]. According to this model, the memory impairment is improved by estrogen and phytoestrogen as similar as the memory impairment induced by menopause[17]. In addition, it is cheap and easy to manage, so it is a suitable model for the assessment the pharmacological effect of various interventions on memory aspect in menopause condition.

Chicken essence, black rice, mulberry and ginger are widely consumed in Asian countries especially in Thailand both as food and as medicine. It has been reported that chicken essence contains abundant dipeptides such as carnosine and anserine which exhibit antioxidant activity[20]. Recent findings also reported that mulberry, ginger and black rice possess antioxidant activity and improve oxidative related brain damage and brain impairments[16,21,22]. In addition, herbs which suppress acetylcholinersterase (AChE) activity can also improve memory impairment[23]. Moreover, according to traditional folklore, it is believed that polyherbal recipe can maximize the health benefit via the synergistic effect. To date, the effect of the supplementation of chicken essence plus black rice and mulberry leaves on memory is still unknown. Therefore, we aimed to determine the memory enhancing effect of "WO1", a polyherbal chicken soup in ovariectomized rats. In addition, the possible underlying mechanism was further investigated via the determination of the effects of "WO1" on cholinergic function and oxidative stress markers in hippocampus, an area playing an important role on learning and memory.

Materials and Methods

Preparation and compositions of WO1

"WO1", a polyherbal chicken soup used in this study, contains decoction of mulberry leaves, black rice, ginger rhizome and chicken essence at a ratio of 2: 1: 1: 2. In brief, all herbal extracts and chicken were mixed at room temperature and then centrifuged at 4,000 g for 20 minutes. After the centrifugation, the supernatant was separated and used for further study. The percent yield of polyherbal soup was 33.33. The concentration of total phenolic compounds was 800 mg GAE/ g sample. The amino acids profiles of "WO1"were shown in Table 1. In addition "WO1" also contained quercetin, cynaidin and gingerol at concentrations of 9.698±0.888 milligram (mg) Quercetin equivalent (QE)/ 100 ml WO1 soup, 0.151±0.004 mg Cyanidin-3-glucoside (Cyn-3-glu)/100 milliliter (ml) WO1 soup and 5.136±0.692 mg 10-gingerol/100 ml WO1 soup as shown in Figure 1.

Animals

Healthy female Wistar rats (200 to 250 g) were purchased from National Laboratory Animal Center, Salaya, Nakhon Pathom and they were housed in group of 6 per cage in standard metal cages at 24±2°C on 10: 14 h light-dark cycle. All rats were permitted to access commercial food pellets and water *ad labium*. The present study was conducted to minimize animal suffering in accordance with the internationally accepted principles for laboratory use and care of European Community (EEC directive of 1986; 86/ 609/EEC). The experimental protocols were approved by the Institutional Animal Care and Use Committee.

Ovariectomy

The rats were anesthetized after fasting for 16 h with thiopental sodium at dose of 50 mg.kg^{-1} BW via intraperitoneal route after 7 days of acclimatization. Then, they were subjected to either bilateral laparotomy or bilateral ovariectomy. In brief, the dorsal mid-lumbar area was shaved and swabbed with surgical scrub, iodine and alcohol. A 2 to 3 cm dorsal midline skin incision was made halfway between the caudal edge of the ribcage and the base of the tail. A single incision of 5.5 to 10 mm long was made into the muscle wall on both the right and left sides approximately 1/3 of the distance between the spinal cord and the ventral midline. The

Table 1. Amino acids profile in WO1

Amino Acid Profile	Results (mg/100 g)
Alanine	7.96
Argenine	<5.00
Aspartic acid	8.71
Cystine	<5.00
Glutamic acid	22.90
Glycine	18.03
Histidine	32.93
Hydroxylysine	<5.00
Hydroxyproline	<5.00
Isoleucine	11.77
Leucine	21.99
Lysine	59.13
Methionine	<5.00
Phenylalanine	20.68
Proline	16.73
Serine	<5.00
Threonine	<5.00
Tryptophan	<5.00
Tyrosine	12.13
Valine	<5.00

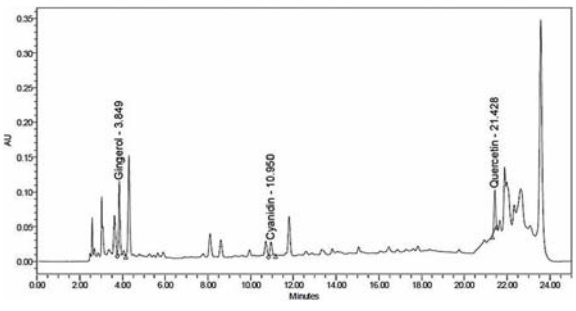


Figure 1. Fingerprint chromatogram of WO1, a polyherbal chicken soup.

ovary and the oviduct were exteriorized through the muscle wall. A hemostat was clamped around the uterine vasculature between the oviduct and uterus. Each ovary and part of the oviduct was removed with single cuts through the oviducts near the ovary. The hemostat was removed and the remaining tissue was replaced into the peritoneal cavity. The ovary on the other side was removed in a similar manner. The muscle wall and skin were closed with absorbable suture.

General procedures

A total 48 female rats were used as experimental animals. Eight rats were sham operated and treated with vehicle and the remaining 40 rats were ovariectomized (OVX) bilaterally. OVX rats were divided into 5 groups. They were treated with vehicle (distilled water), isoflavone (Genistein 15 mg.kg^{-1}) and polyherbal recipe (0.8, 1.6, 2.4 mg.kg^{-1}) for 35 days. The animals were determined learning and memory using Morris water maze test every 7 days throughout the study period. At the end of experiment, rats were sacrificed, hippocampi were isolated and determined oxidative stress markers including malondialdehyde (MDA) level and the activities of superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPX) enzymes. In addition, the activity of acetylcholinesterase (AChE) in hippocampus was also determined and used as indirect indicator for the cholinergic activity.

Determination of oxidative stress markers and acetylcholinesterase activity

Hippocampal homogenate was prepared. In brief, the brain tissues were weighed and homogenized with a buffer consisting of 10 mM sucrose, 10 mM Tris-HCl, and 0.1 m M EDTA (pH 7.4). Then the brain homogenates were centrifuged at 3,000 g for 15 min at 4°C. The supernatant was used for bioassays. The level of malondialdehyde (MDA) in hippocampus was determined by determining the accumulation of thiobarbituric acid reactive substances (TBARSs) according to the method of Ohkawa et al[24]. The activities of superoxide dismutase (SOD) activity was determined by the method of McCord and Fridovich[25] while catalase and glutathione peroxidase activities were determined by method of Aebi et al[26] and Dundar et al[27] respectively. The activity of acetylcholinesterase (AChE) was evaluated using Ellman method[28].

Determination of memory enhancing effect

The effect of "WO1" on spatial memory was evaluated by using Morris water maze test[29]. The apparatus was a pool with 170 cm diameter filled up with tap water for 40 cm deep and the water surface was covered with nontoxic powder. The pool was divided into four quadrants and the removable escape platform was placed in the center on one quadrant below the water level. The location of the platform was invisible and it remained there throughout the training. Each rat must memorize the environment cues to locate the platform. The animal was placed in the water in the starting quadrant and allowed to swim until it found and climbed onto the platform. The time which the animal spent to reach the hidden platform was recorded as escape latency. The retention time was determined 24 h later by allowing the animal to be subjected to the same situation as mentioned earlier except that the immersed platform was removed and the time which the animal spent for swimming in the quadrant previously located platform was regarded as retention time.

Statistical analysis

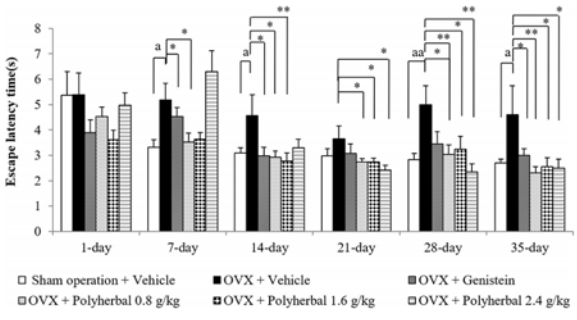
All data were expressed as means ± SEM and analyzed statistically by one-way ANOVA, followed by post hoc (LSD) test. The results were considered statistically significant at p-value <0.05.

Results

Effect of "WO1", a polyherbal chicken soup, on spatial memory

Figure 2 showed that ovariectomized rats which received vehicle significantly enhanced the escape latency after single administration and at 4, 14, 28 and 35 days of intervention (p-value <0.01, 0.05, 0.01 and 0.05, respectively; compared with sham operation plus vehicle). Ovariectomized rats which received Genistein, a soy-derived isoflavone and phytoestrogen with potent antioxidant and memory enhancing effects[31], could attenuate the elevation of escape latency induced by bilateral ovariectomy at 14, 28 and 35 days of intervention (p-value <0.05 all; compared with OVX plus vehicle). Ovariectomized rats which received low and medium doses of "WO1" (0.8 and 1.6 g.kg^{-1}) could attenuate the enhanced escape latency at 7, 14, 21, 28 and 35 days of intervention (p-value <0.05 all; .05 and 0.01; 0.05 all; 0.01 and 0.05; 0.01 and 0.05 respectively; compared with OVX plus vehicle). However, high dose of "WO1" could significantly decrease the enhanced escape latency of OVX rats at 21, 28 and 35 days (p-value <0.05, 0.01 and 0.05, respectively; compared with OVX plus vehicle).

The effect of "WO1" on retention time in OVX



[a,aa] p-value<0.05 and 0.01 respectively (compared with sham plus vehicle), *,** p-value<0.05 and .01 respectively (compared with OVX plus vehicle)

Figure 2. Effect of "WO1", a polyherbal chicken soup, on escape latency in Morris water maze test of ovariectomized rats. Data were presented as mean ± SEM (n = 6 per group).

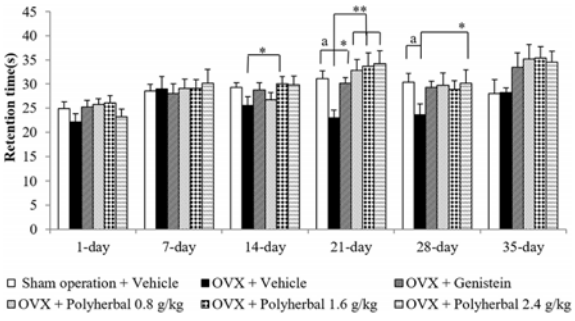
rats was also evaluated and results were shown in Figure 2. OVX rats which received vehicle showed the decreased retention time at 21 and 28 days of intervention (p-value <0.05 all; compared with sham plus vehicle). OVX rats which received either Genistein or low dose of "WO1" significantly attenuated the decreased retention time induced by OVX at 21 days of intervention (p-value <0.05 and 0.01 respectively; compared with OVX plus vehicle). In addition, it was also found that OVX rats which received medium dose of "WO1" attenuated the reduction of retention time induced by ovariectomy at 14 and 21 days of treatment (p-value <0.05 and 0.01, respectively; compared with OVX plus vehicle) whereas OVX rats which received high dose of "WO1" produced the significant mitigation effect on retention time induced by OVX at 21 and 28 days of intervention (p-value <0.01 and 0.05, respectively; compared with OVX plus vehicle).

Effect of "WO1" on AChE activity

Based on the suppression effect of AChE on memory mentioned earlier[23], the authors also investigated the effect of "WO1" on AChE activity in hippocampus and results were shown in Figure 3. It was found that OVX rats which received vehicle showed the elevation of AChE activity (p-value <0.01; compared with sham plus vehicle) in hippocampus. Interestingly, OVX rats which received Genistein failed to mitigate the elevation of AChE induced by ovariectomy whereas OVX rats which received "WO1" at all doses used in this study significantly attenuated the elevation of AChE induced by ovariectomy in hippocampal area (p-value <0.001 all; compared with OVX plus vehicle).

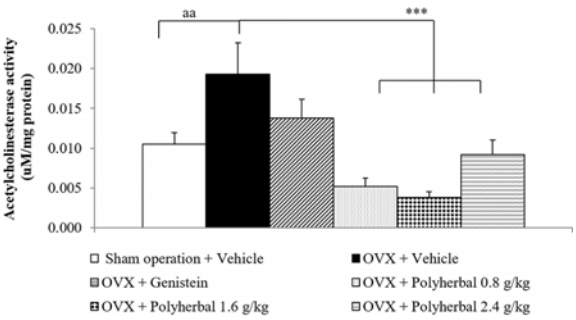
Effect of "WO1" on oxidative stress markers

The effects of polyherbal recipe on various oxidative stress markers in hippocampus are shown in Figure 4 to 8. Ovariectomized rats significantly decreased SOD activity but increased level MDA in hippocampus (p-value <0.001 and 0.01, respectively; compared with sham operation plus vehicle). Ovariectomized rats which received Genistein significantly enhanced SOD, CAT but decreased MDA level (p-value <0.05, 0.001 and 0.01 respectively; compared with ovariectomized plus vehicle). It was found that ovariectomized rats which received "WO1" at doses of 0.8, 1.6 and 2.4 $g.kg^{-1}$ significantly enhanced SOD activity (p-value <0.01, 0.05 and 0.05 respectively; compared with OVX plus vehicle) but decreased MDA level in hippocampus (p-value <0.01, 0.001 and 0.05 respectively; compared with OVX plus vehicle). However, only ovariectomized rats which received high dose of "WO1" showed the enhanced CAT and GPx activities in hippocampus (p-value <0.05 and 0.001 respectively; compared with OVX plus vehicle).



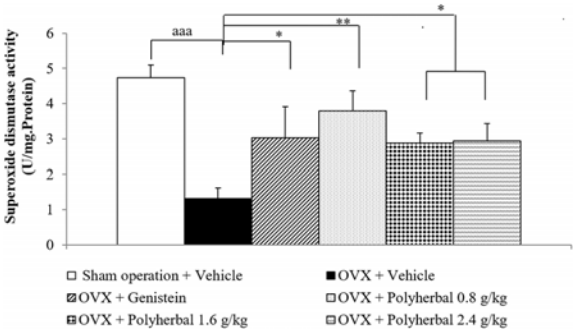
[a,aa] p-value <0.05 and 0.01 respectively (compared with sham plus vehicle), *,** p-value <0.05 and 0.01 respectively (compared with OVX plus vehicle)

Figure 3. Effect of 'WO1", a polyherbal chicken soup, on retention time in Morris water maze test of ovariectomized rats. Data were presented as mean ± SEM (n = 6 per group).



[aa] p-value <0.01 (compared with sham plus vehicle), *** p-value <0.001 (compared with OVX plus vehicle)

Figure 4. Effect of "WO1", a polyherbal chicken soup, on the activity of acetylcholineaterase (AChE) in hippocampus of ovariectomized rats. Data were presented as mean ± SEM (n = 6 per group).



[aaa] p-value <0.001 (compared with sham plus vehicle), *,** p-value <0.05 and 0.01 respectively (compared with OVX plus vehicle)

Figure 5. Effect of polyherbal chicken soup "WO1" on the activity of superoxide dismutase (SOD) in hippocampus of ovariectomized rats. Data were presented as mean ± SEM (n = 6 per group).

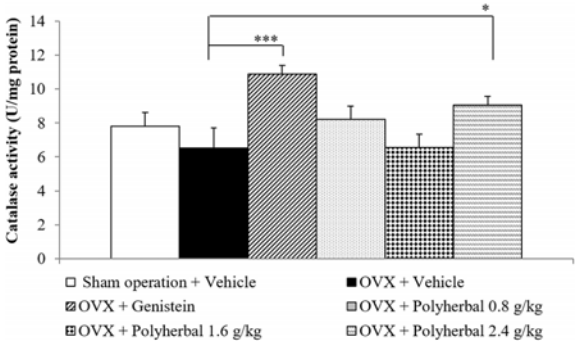
Discussion

The current results show that polyherbal chicken soup "WO1" at all doses used in this study enhanced memory performance together with the suppression of AChE activity and decreased oxidative stress.

Since OVX animal has been regarded as a validated animal model of hormone deprivation to study post-menopausal changes in adult female, it has been used as a tool to test the effect of "WO1" on memory, cholinergic function and oxidative stress status in hippocampus. Our results showed that OVX rats which received vehicle exhibited memory impairment together with the increased oxidative stress status in hippocampus. This change was in agreement with previous study[17,31]. It has been shown that the elevated oxidative stress in hippocampus of OVX rats was attributed partly to the decreased SOD activity in the aforementioned area. Based on the previous findings that the decreased oxidative status in hippocampus was responsible for improved memory[32], the effects of "WO1" on the oxidative stress markers including MDA level and the activities of SOD, CAT and GPx activities were also investigated. The current results were also in correspondence with the previous findings which demonstrated that substances contained abundant substances possessing antioxidant could improve oxidative stress status and improved memory[17,31,32].

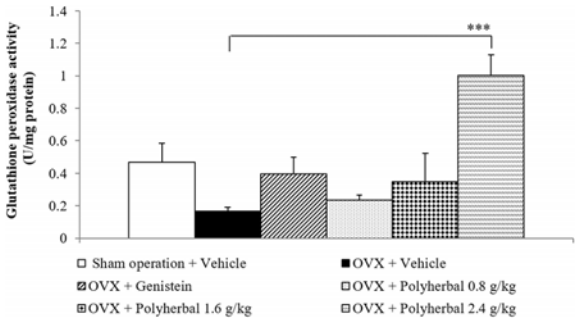
Cholinergic system is also regarded as one neurochemical system which plays an important role on memory impairment in OVX animals. The herbal extracts which suppress AChE leading to the enhanced cholinergic function and improved memory impairment in OVX animals[33]. Our results also clearly demonstrated that "WO1" at all doses used in the present study also suppressed AChE activity in hippocampus of OVX rats. Therefore, this effect might be responsible in part for the memory enhancing effect of "WO1" observed in the present study.

"WO1" contained many substances which exert cognitive enhancing effect via an antioxidant effect and AChE suppression activity such as quercetin, gingerol and anthocyanin[9-16]. In addition, both quercetin and anthocyanin also possess estrogenic activity such as quercetin[34], anthocyanin[35]. It has been reported that estrogenic activity is associated with the neuroprotective and cognitive enhancing effects[36]. Although, 'WO1 also contained many amino acids which has influence on learning and memory function, the levels of amino acid which could exhibit the memory enhancing effect such as glutamic acid, tyrosine, typtophan[37], the levels of the mentioned amino acids are too low to exert the cognitive enhancing effect Therefore, the cognitive enhancing effect and neuroprotective effect of 'WO1" might involve quercetin, gingerol and anthocyanin rather than the amino acids



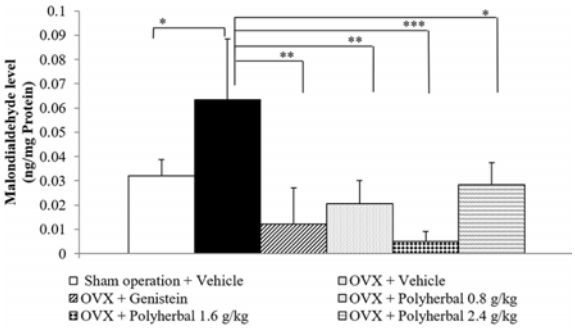
*,*** *p*-value <0.05 and 0.001 respectively (compared with OVX plus vehicle)

Figure 6. Effect of polyherbal chicken soup "WO1" on the activity of catalase (CAT) in hippocampus of ovariectomized rats. Data were presented as mean ± SEM (n = 6 per group).



*** *p*-value <0.001 (compared with OVX plus vehicle)

Figure 7. Effect of polyherbal chicken soup "WO1" on the activity of glutathione peroxidase (GPx) in hippocampus of ovariectomized rats. Data were presented as mean ± SEM (n = 6 per group).



[a] *p*-value <0.05 (compared with sham plus vehicle), *,**,*** *p*-value <0.05, 0.01 and 0.001 respectively (compared with OVX plus vehicle)

Figure 8. Effect of polyherbal chicken soup "WO1"on the level of malondialdehyde (MDA) in hippocampus of ovariectomized rats. Data were presented as mean ± SEM (n = 6 per group).

mentioned earlier. However, the interaction effect among various substances could not be eliminated.

No dose dependent manner of "WO1" was observed in this study. The possible explanation was due to the influences of multi-factors on the observed parameters. Therefore, no simple linear relationship between the concentration of "WO1" and the observed parameters were observed.

Conclusion

The current results demonstrated that "WO1" a polyherbal chicken soup, can improve memory deficit in experimental menopause. The possible mechanism might occur partly via the reduction of oxidative status but increased the cholinergic system function in the hippocampus. The possible active ingredients may possibly relate to quercetin, gingerol and anthocyanins contents. However, further studies about the metabolomics of "WO1" and clinical trials are still required.

What is already known on this topic?

The decreased estrogen levels during menopause is related with the enhanced oxidative stress which occurs as the result of the imbalance between the formation of the reactive oxygen species and the buffering capacity of antioxidant system. Dietary supplements which are rich in antioxidants can protect against oxidative stress related memory impairment.

What this study adds?

"WO1" a polyherbal chicken soup improve memory deficit in experimental menopause partly via the reduction of oxidative status but increased the cholinergic system function in.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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ซุปไก่ผสมสมุนไพรหลายชนิดแบบใหม่ทำให้ความจำ ความเครียดออกซิเดชัน และการทำงานของระบบประสาทโคลิเนอร์จิคในฮิปโปแคมปัสของสัตว์ทดลองที่จำลองภาวะวัยทอง

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ภูมิหลัง: แม้ภาวะความจำบกพร่องในวัยหมดประจำเดือนจะทวีความสำคัญเพิ่มขึ้นแต่การรักษาความจำบกพร่องในวัยหมดประจำเดือนที่ใช้ในปัจจุบันยังมีข้อจำกัด ดังนั้นสารเพิ่มความจำสำหรับวัยหมดประจำเดือนจึงยังเป็นที่ต้องการ สืบเนื่องจากบทบาทสำคัญของความเครียดออกซิเดชัน และการทำงานของระบบประสาทโคลิเนอร์จิคต่อความจำและแนวความคิดเรื่องการเสริมฤทธิ์กันของสารทำให้ฤทธิ์เพิ่มความจำของซุปไก่ผสมสมุนไพรหลายชนิดซึ่งมีสมุนไพรหลายชนิดที่มีฤทธิ์ต้านอนุมูลอิสระได้รับความสนใจ อย่างไรก็ตามในปัจจุบันยังไม่มีหลักฐานสนับสนุน

วัตถุประสงค์: เพื่อประเมินฤทธิ์เพิ่มความจำและกลไกการออกฤทธิ์ที่น่าจะเป็นได้ของซุปไก่ผสมสมุนไพรหลายชนิด (WO1) ในสัตว์ทดลองที่เป็นแบบจำลองวัยทอง

วัสดุและวิธีการ: จะแบ่งสัตว์ทดลองเพศเมียพันธุ์วิสตาร์เป็น 6 กลุ่ม 1) กลุ่มที่ได้รับการผ่าตัดหลอกและได้รับสารนำส่ง 2) กลุ่มที่ได้รับการผ่าตัดรังไข่และได้รับสารนำส่ง 3) กลุ่มที่ได้รับการผ่าตัดรังไข่และได้รับสาร isoflavone 4 ถึง 6) กลุ่มที่ได้รับการผ่าตัดรังไข่และได้รับ WO1 ขนาด 0.8, 1.6 และ 2.4 มิลลิกรัมต่อกิโลกรัมน้ำหนักตัวตามลำดับ สัตว์ทดลองทุกตัวจะได้รับสารที่กำหนดเป็นเวลา 35 วันและจะประเมินความจำทุก 7 วันตลอดการทดลอง จากนั้นจะวัดระดับ malondialdehyde (MDA) ร่วมกับการทำงานของ superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) และ acetylcholinesterase (AChE) ในฮิปโปแคมปัสเมื่อสิ้นสุดการทดลอง

ผลการศึกษา: WO1 ทุกขนาดจะเพิ่มความจำและลดการทำงานของ AChE และระดับ MDA ในฮิปโปแคมปัสของหนูที่ถูกตัดรังไข่ หนูทุกกลุ่มที่ได้รับ WO1 จะมีการทำงานของ SOD เพิ่มขึ้นแต่การเพิ่มการทำงานของ CAT และ GSH-Px จะพบเพียงในหนูกลุ่มที่ได้รับ WO1 ขนาดสูง

สรุป: WO1 สามารถเพิ่มความจำในภาวการณ์จำลองวัยหมดประจำเดือน กลไกส่วนหนึ่งน่าจะเกิดผ่านการทำให้การทำงานของระบบประสาทโคลิเนอร์จิคและภาวะความเครียดออกซิเดชันในฮิปโปแคมปัสดีขึ้น ข้อมูลของเราแสดงให้เห็นว่า WO1 เป็นอาหารสุขภาพที่มีเป้าหมายเพื่อเพิ่มความจำที่มีศักยภาพสำหรับวัยทอง อย่างไรก็ตามการศึกษาทางคลินิกเพื่อยืนยันประโยชน์ต่อสุขภาพที่กล่าวข้างต้นยังคงจำเป็น