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FULL COMMUNICATION

Gastrodia elata Bl. Attenuated Learning Deficits Induced by Forced-Swimming Stress in the Inhibitory Avoidance Task and Morris Water Maze

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ABSTRACT This study adopted the forced-swimming paradigm to induce depressive symptoms in rats and evaluated the effects on learning and memory processing. Furthermore, the effects of the water extract of *Gastrodia elata* Bl., a well-known Chinese traditional medicine, on amnesia in rats subjected to the forced-swimming procedure were studied. Rats were subjected to the forced-swimming procedure, and the inhibitory avoidance task and Morris water maze were used to assess learning and memory performance. The acquisition of the two tasks was mostly impaired after the 15-minute forced-swimming procedure. Administration of the water extract of *G. elata* Bl. for 21 consecutive days at a dosage of 0.5 or 1.0 g/kg of body weight significantly improved retention in the inhibitory avoidance test, and the lower dose showed a better effect than the higher one and the antidepressant fluoxetine (18 mg/kg of body weight). In the Morris water maze, the lower dose of the water extract of *G. elata* Bl. significantly improved retention by shortening escape latency in the first test session and increasing the time in searching the target zone during the probe test. These findings suggest that water extracts of *G. elata* Bl. ameliorate the learning and memory deficits induced by forced swimming.

KEY WORDS: • ***amnesia*** • ***antidepressant*** • ***Chinese medicine*** • ***learning*** • ***memory***

INTRODUCTION

Major depression is one of the most common mental disorders. In the United States, lifetime prevalence is about 10–20%.[1] The lifetime suicide attempt rate is greater than 15% in patients suffering from major depression.[2] Therefore, major depressive disorder, with high morbidity and mortality, is estimated to be the second greatest cause of disability worldwide.[3] Medication is the most commonly therapeutic strategy used, but pharmacological efficacy varies from patient to patient. The numerous adverse effects and long treatment course of antidepressants contribute to poor compliance.[4,5] Therefore, it is imperative to search for alternative treatments with equivalent or better efficacy and fewer side effects. In this regard, Chinese medicine may possess a high potential for treating depression.

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Gastrodiae rhizome, known as *Tianma* in Chinese, is the dried tuber of *Gastrodia elata* Bl. It is a traditional Chinese medicine officially listed in the *Chinese Pharmacopoeia*[6] that has been well known for centuries in treating dizziness, epilepsy, paralysis, and convulsions. Gastrodin, *p*-hydroxybenzylaldehyde, vanillyl alcohol, and *p*-hydroxybenzyl alcohol are the major active components of *G. elata* Bl.[7–11] Many biological functions of *G. elata* Bl. are documented by previous studies, such as anticonvulsant,[12,13] antioxidant and free radical scavenging,[14,15] neuroprotectant,[13,16,17] learning improvement,[18,19] anxiolytic,[20] and antidepressant[21] properties. We previously demonstrated that the water extract of *G. elata* Bl. (WGE) has antidepressant effects in rats subjected to acute and subchronic forced-swimming tests, an animal model of depression, and that it alters the monoamine concentration and metabolism in the rat brain.[22,23]

Memory impairment is a common problem affecting patients with depression.[24,25] Chronic stress may alter neuronal properties in the hippocampus, including morphology, plasticity, and receptor functions,[26] which not only induce the depression state[27,28] but also disturb

cognitive processes[29,30] such as learning and memory. Antidepressants have been shown to attenuate learning and memory deficits in both animal and clinical studies of depression.[31,32]

The objectives of this study were to establish an animal model of depression-induced amnesia by evaluating the effects of the forced-swimming procedure on the learning and memory function in rats and then to evaluate the effects of WGE on learning and memory deficits.

MATERIALS AND METHODS

Materials and chemicals

WGE was obtained from Koda Pharmaceutical Co. Ltd. (Taoyuan, Taiwan). Five kilograms of crude *G. elata* Bl. was extracted with 35 and 25 L of boiling water for 1 hour and 50 minutes, respectively. The extract was filtered and freeze-dried. Total yield was 944.2 g (18.9%). The freeze-dried WGE was authenticated by a high-performance liquid chromatography system (model D-700 interface, model L-7100 pump, and model L-7420 ultraviolet-visible detector, Hitachi Instruments Service Co., Ltd., Ibaraki-ken, Japan) using vanillyl alcohol as a standard. Fluoxetine (Prozac®) was provided by Eli Lilly and Co. (Taipei, Taiwan).

Animals

Four-week-old male Sprague–Dawley rats were purchased from BioLasco Taiwan Co., Ltd. (Taipei). The rats were housed in an animal room with a controlled light cycle (12-hour light/dark), temperature (23 ± 2°C), and humidity (60 ± 10%). Rats were pair-housed in wire-mesh cages with free access to food rodent chow and water.

Behavioral tasks

Three behavior tasks were used in this study. The apparatus, procedure, and index adopted for each task are described as follows:

The forced-swimming procedure. The forced-swimming procedure followed the forced-swimming test developed by Porsolt *et al.*,[33] which is commonly used for antidepressant efficacy assessment in animals.[34] The forced-swimming test consists of two sessions: a pretest session followed by a test session 24 hours later. Rats were placed into a glass cylinder (20 cm in diameter) filled with 30 cm of room temperature water for 15 minutes and 5 minutes during the pretest and test sessions, respectively. Modeling the despair state seen in depression patients, the inescapable environment encountered in the pretest session forged the helpless behavior (immobility) in the later test session. Accordingly, this study used the forced-swimming test pretest session to induce a depressive-like state in rats.

The inhibitory avoidance task. The inhibitory avoidance apparatus is a trough-shaped alley (90 cm long, 15 cm deep, 25 cm wide at the top, and 6 cm wide at the floor with a slit along the center) divided into a light compartment and a dark compartment with a guillotine door. The light compartment was illuminated with an incandescent bulb; the dark compartment was unlit. During the pre-exposure session, a rat was placed in the light compartment facing away from the door. When the rat turned around to face the door, the sliding door was opened, and the rat was allowed to move into the dark compartment. After the rat was in the dark compartment with its four paws, the door was closed. The rat was then removed from the apparatus and placed back into its cage. During the training session, the procedure was identical to that of the pre-exposure session except that an inescapable electric foot shock (0.5 mA, 1 second) was given after the rat entered the dark compartment. After the shock, the rat was removed from the apparatus and returned to its cage. The test session was conducted 24 hours after the training stage to test rat memory. As in the previous two sessions, the rat was introduced into the light compartment during the test session. The time elapsing from turning around until stepping into the dark compartment completely was recorded. The duration was noted as the step-through latency and used as an index of memory; the longer the latency, the better the retention performance. If the rat did not move into the dark compartment within 600 seconds, the test trial was terminated, and step-through latency was assigned as 600 seconds. No foot shock was delivered in the test session.

The Morris water maze. The apparatus was a black plastic circular pool (200 cm in diameter, 60 cm in height) located in the middle of a room with distinctive cues in space. The pool was filled with 50 cm of room temperature water. The pool was subdivided into four equal quadrants. A transparent platform was placed 1.5 cm beneath the surface of the water at the center of a fixed quadrant. The behavior of rats in the pool was automatically recorded and analyzed by the EthoVision system (Noldus Information Technology, Wageningen, The Netherlands). In the pre-exposure session, a rat was introduced into the pool without the platform from a randomly selected quadrant. After freely swimming in the pool for 2 minutes, the rat was picked up, warmed to dry, and returned to its original cage. The training stage of this study included two four-trial sessions at 24-hour intervals. In each session, the rats received four trials by randomly entering the pool in the four different quadrants. In each trial, a rat was placed in the water and allowed to swim for 120 seconds or until it reached the platform and climbed onto it. The time a rat took in locating the platform was recorded as the escape latency. If the rats did not find the platform in 120 seconds, they were placed on the platform. Each rat stayed on the platform for 60 seconds and then was returned to its cage for 20 seconds before the next trial. After each training session, the rat was warmed to dry by a heater and placed back in its original cage. The test session, including a general test and a probe test, was conducted the day after the training session. The general test contained three trials. A rat was placed into the pool in the three different quadrants (except for the target quadrant in which the

platform was located) and allowed to freely swim for 120 seconds or until it reached the platform. Once the rat arrived at the platform or after 120 seconds of swimming, it was returned to its cage for 80 seconds before the start of the next trial. After three trials, rats were warmed, dried, and returned to the cage. Escape latency was recorded as the index of a rat's retention performance: the better the spatial memory, the shorter the escape latency. Immediately following the general test, a probe test was administered. In the probe test, the platform was removed from the pool, and the rat was placed into the pool at the opposite quadrant of the target and allowed to swim freely for 120 seconds. The swimming duration spent in each quadrant was calculated by the EthoVision system. The relative amount of time in searching the quadrant in which the platform was located before was taken as another index of retention performance.

Experiment 1: Effects of forced swimming on the inhibitory avoidance task (Experiment 1-1) and the Morris water maze (Experiment 1-2)

For both the inhibitory avoidance task and the Morris water maze, rats were randomly assigned to one of four groups: the control, pre-training, post-training, and pre-test groups. The two learning tasks were executed as described. Rats were subjected to the 15-minute forced-swimming procedure 5 minutes before training, 5 minutes after training, or 5 minutes before the testing and designated as the pre-training, post-training, and pre-test groups. In addition to the groups undergoing the forced-swimming procedure, rats in the other three groups were placed in the glass cylinder filled with 5 cm of water for 15 minutes at the same time points. After the forced-swimming procedure, rats were removed from the water and immediately warmed to dry with an electric heater. Afterward, rats were placed back into their cages. The experimental protocol is shown in Figure 1.

Experiment 2: Effects of G. elata Bl. on the inhibitory avoidance task (Experiment 2-1) and the Morris water maze (Experiment 2-2) after the forced-swimming procedure

Rats were randomly assigned to one of four groups: the control, LWGE, HWGE, and Fluoxetine groups, which received deionized water (10 mL/kg of body weight), low-dose WGE (0.5 g/kg of body weight), high-dose WGE (1.0 g/kg of body weight), and fluoxetine (18 mg/kg of body weight) for 21 consecutive days. WGE and fluoxetine were dissolved in deionized water; all samples were administered by oral gavage. Pre-exposure and training sessions of the inhibitory avoidance task were performed on Days 20 and 21, while the test session was held on Day 22. In the Morris water maze, pre-exposure, first training, second training, and test sessions were carried out on Days 19, 20, 21, and 22. Rats in all groups underwent a 15-minute forced-swimming procedure 5 minutes before the training session of each learning task. The experimental protocol is shown in Figure 1.

Statistical analysis

Data from the inhibitory avoidance task were calculated for median ± interquartile range of each group because 600 seconds was the cutoff latency of stepping-through for a truncated distribution. Nonparametric statistics were used to analyze data. Results from the Morris water maze were calculated for mean ± SD values from each group. Data were analyzed by one-way analysis of variance and Duncan's multiple tests. A P value of $< .05$ was considered to be statistically significant.

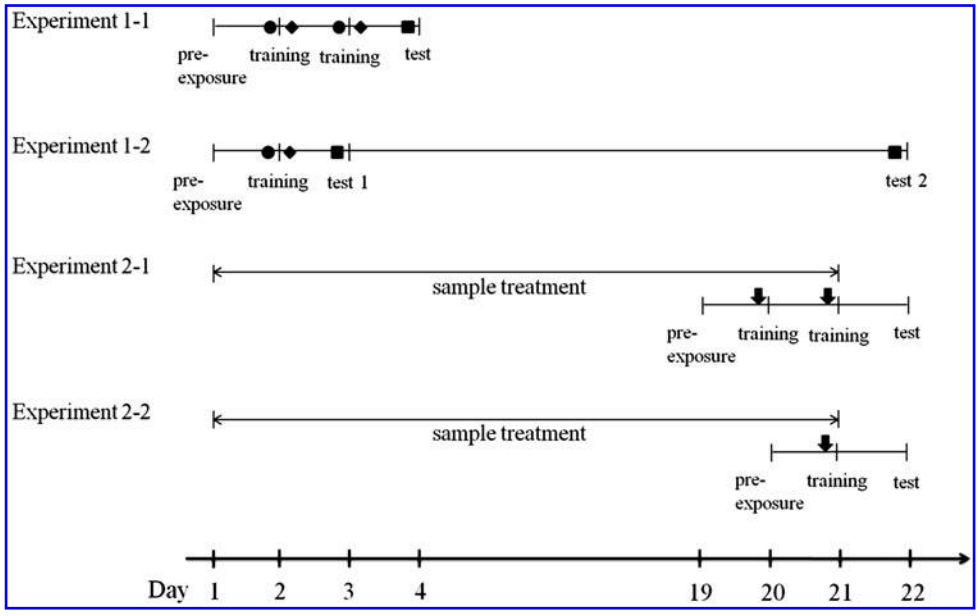

FIG. 1. Schematic diagram for the experimental protocol. (Experiment 1-1 and 1-2) Influences of forced swimming on learning and memory performance administered at different time points in the inhibitory avoidance task and Morris water maze, respectively. (Experiment 2-1 and 2-2) Effect of *G. elata* Bl. on acquisition deficit induced by forced swimming in the inhibitory avoidance task and Morris water maze, respectively. In Experiment 1, rats underwent a 15-minute forced-swimming procedure 5 minutes before training (●), 5 minutes after training (◆), and 5 minutes before the test (■) in the pre-training, post-training, and pre-test groups, respectively. In Experiment 2, all rats underwent the 15-minute forced-swimming procedure 5 minutes before training (⬇).

RESULTS

Experiment 1-1: Influences of forced swimming on learning and memory performance administered at different time points in the inhibitory avoidance task

In this experiment, rats underwent a 15-minute forced-swimming procedure before training, after training, and before testing. Figure 2 shows the retention performance for the test sessions conducted on Test 1 (the first day after the training session) and Test 2 (day 20 after the training session). In Test 1, step-through latency in the pre-training group was significantly shorter than in the control group ($P < .01$). Step-through latency in the control, post-training, and pre-test groups all reached the ceiling score, 600 seconds. In other words, the post-training group and pre-test group did not differ from the control group. The data suggest that the forced-swimming procedure significantly impairs acquisition of an inhibitory avoidance response, but no effects were observed in Test 1 on the consolidation or retrieval of the inhibitory avoidance memory. To further clarify the effects of forced-swimming on consolidation and retrieval, Test 2 was conducted. In Test 2, the step-through latency in the control group was significantly lower than that in Test 1 ($P < .01$). Performance in the pre-training group in Test 2 appeared to be lower than in Test 1, but failed to reach statistical significance. In the post-training and pre-test groups, rats still did not cross into the dark compartment after 10 minutes and thus had significantly longer retention latencies than rats in the control group ($P < .01$). This suggests that consolidation and retrieval of inhibitory avoidance memory were enhanced by forced swimming in a 20-day test.

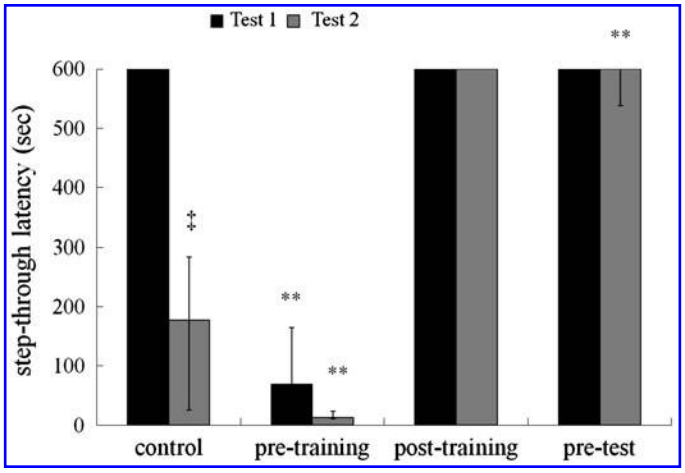

FIG. 2. Step-through latency in the inhibitory avoidance task of rats subjected to forced swimming at various time points. Data are median ± interquartile range values ($n = 9$). Pre-training, post-training, and pre-test groups were exposed to the 15-minute forced-swimming procedure 5 minutes before training, after training, and before testing of the inhibitory avoidance task, respectively. Performance in the retention tests given in Test 1 (the first day after training) and Test 2 (day 20 after training) are shown. **Significantly different from the control group ($P < .01$), ‡significantly different from Test 1 performance ($P < .01$), all based on nonparametric statistics.

Experiment 1-2: Influences of forced swimming on learning and memory performance administered at different time points in the Morris water maze task

In this experiment, rats in various groups were forced to swim for 15 minutes before training, after training, or before a test session. Escape latencies in the two training sessions and the general test session are shown in Figure 3. In the first training and test sessions, rats in the pre-training group spent more time reaching the platform compared with the control group ($P < .05$), whereas the other two groups did not differ significantly from the control. Escape latencies of the control and pre-training groups significantly decreased in the second training session and test session in comparison with those in the first training session ($P < .05$). Comparing escape latency from the first trial in the test session, the pre-training group showed the worst performance followed by the pre-test group (data not shown). Escape latencies in these two groups were significantly longer than that in the control group ($P < .05$). Figure 4 shows the swimming time spent in the opposite and target quadrants. There was no significant difference in the swimming time in the opposite zone among the groups. By contrast, rats in the pre-training group spent less time in the target quadrant than the other groups ($P < .05$). All rats except for those in the pre-training group spent a longer time searching the target quadrant than the opposite quadrant ($P < .05$).

Experiment 2-1: Effect of G. elata *Bl. on acquisition deficit induced by forced swimming in the inhibitory avoidance task*

According to the results from Experiment 1-1, 15 minutes of forced swimming introduced 5 minutes before the

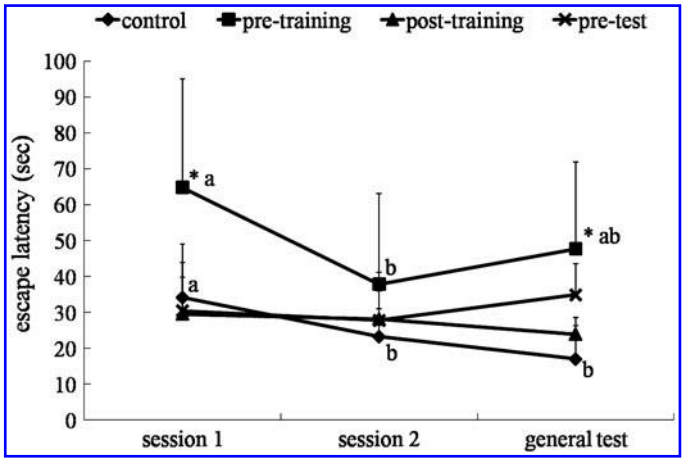

FIG. 3. Escape latency in the Morris water maze of rats subjected to forced swimming at various time points. Data are mean ± SD values ($n = 9$). Pre-training, post-training, and pre-test groups were exposed to the 15-minute forced-swimming procedure before or after training or before testing of the Morris water maze, respectively. [ab]Data not sharing the same letter are significantly different from one another in each group ($P < .05$) by analysis of variance and Duncan's multiple range test. *Significantly different from the control group ($P < .05$).

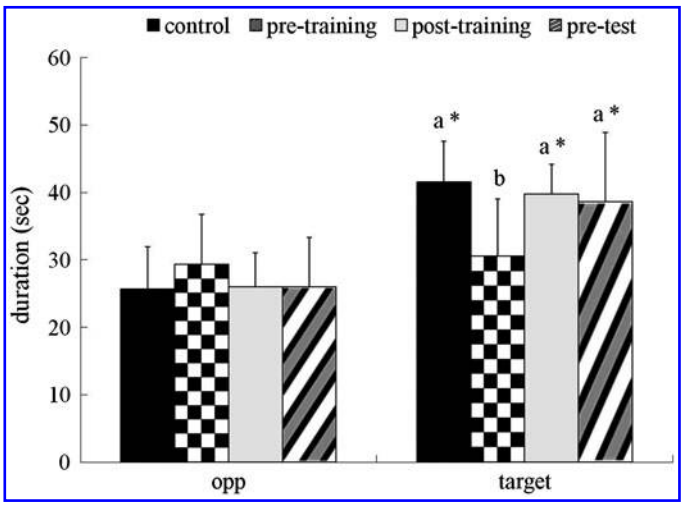

FIG. 4. Swimming duration spent in the target and opposite (opp) quadrants in the Morris water maze of rats subjected to forced swimming at various time points. Data are mean ± SD values ($n = 9$). Pre-training, post-training, and pre-test groups were exposed to the 15-minute forced-swimming procedure 5 minutes before or after training or before testing of the Morris water maze, respectively. Data analysis was performed using analysis of variance and Duncan's multiple range test. [ab]Groups not sharing the same letter are significantly different from one another in the duration spent in the target quadrant ($P < .05$); the duration of time spent in the opp quadrant was not different among the groups. *Significantly different compared with the duration spent in the opp quadrant ($P < .05$).

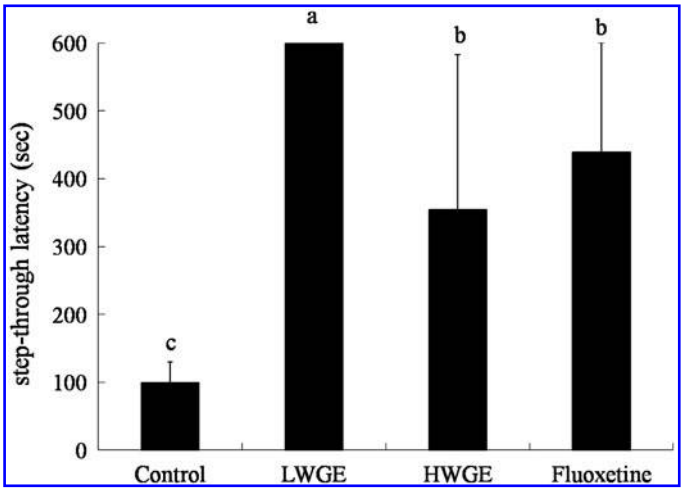

FIG. 5. Effect of *G. elata* Bl. on step-through latency in the inhibitory avoidance task of rats experiencing forced swimming before training. Data are median ± interquartile range values ($n = 12$). All samples were administered for 21 days by oral gavage at the following dosages: Control, 10 mL/kg of body weight deionized water; LWGE, low-dose water extract of *G. elata* Bl. (0.5 g/kg of body weight); HWGE, high-dose water extract of *G. elata* Bl. (1.0 g/kg of body weight); and Fluoxetine, fluoxetine (18 mg/kg of body weight). [abc]Data not sharing the same letter are significantly different from one another ($P < .05$) according to nonparametric statistics.

training session impairs rat performance in the inhibitory avoidance task. Therefore, this study examined whether the impairing effect of forced swimming before training on acquisition of the inhibitory avoidance response can be attenuated by WGE. The results are shown in Figure 5. The step-through latency in the control group was significantly shorter ($P < .05$) than in the LWGE, HWGE, or Fluoxetine groups receiving 0.5 g/kg of body weight WGE, 1.0 g/kg of body weight WGE, or 18 mg/kg of body weight fluoxetine, respectively, for 21 days. Step-through latency in the LWGE group reached the ceiling score of 600 seconds, which is significantly longer than the other three groups ($P < .05$).

Experiment 2-2: Effect of G. elata *Bl. on acquisition deficit induced by forced swimming in the Morris water maze*

The data from Experiment 1-2 reveal that rat spatial memory is significantly impaired when the 15-minute forced-swimming procedure was given 5 minutes before the training session. Accordingly, the forced-swimming procedure was introduced before the training phase in this part as well, and the attenuating effect of WGE was assessed. Escape latencies in the first and second training sessions as well as in the general test session are shown in Figure 6. The escape latencies in all groups in all sessions did not differ from the control, except for the HWGE group in the first training session ($P < .01$). Although rats in the HWGE group showed worse learning and memory, their memory function was significantly improved during these 3 days ($P < .05$). The escape latency of the control and LWGE groups was significantly lower in the test session than in the training sessions ($P < .05$). The memory function of the Fluoxetine group showed no significant improvement over these three sessions. In the first test trial, the escape latency in the LWGE group was significantly shorter than all other groups ($P < .05$) (data not shown). Swimming duration in the opposite and target quadrants in the probe test is shown in Figure 7. There was no difference in the swimming time spent in the opposite zone for all groups. Rats in the LWGE and HWGE groups spent more time in the target quadrant than in the opposite quadrant ($P < .01$ and $P < .05$, respectively), and rats in the LWGE group spent more time in the target zone than all other groups ($P < .05$). Data from this experiment reveal that 0.5 g/kg of body weight WGE administration for 21 days significantly improved rat spatial memory function impaired by the forced-swimming procedure given before the training session.

DISCUSSION

The World Health Organization estimates major depressive disorder to be the second greatest single cause of disability worldwide.[3] Previous studies have found that WGE possesses antidepressant effects as assessed by an animal model of depression, the forced-swimming test.[22,23] As amnesia is one of the symptoms of depression,[24,25] this study investigated if WGE can attenuate learning and memory deficits induced by forced swimming in two tasks. The study first verified the validity of our adopted animal model by showing that a pre-training forced-swimming experience indeed impaired acquisition in two learning

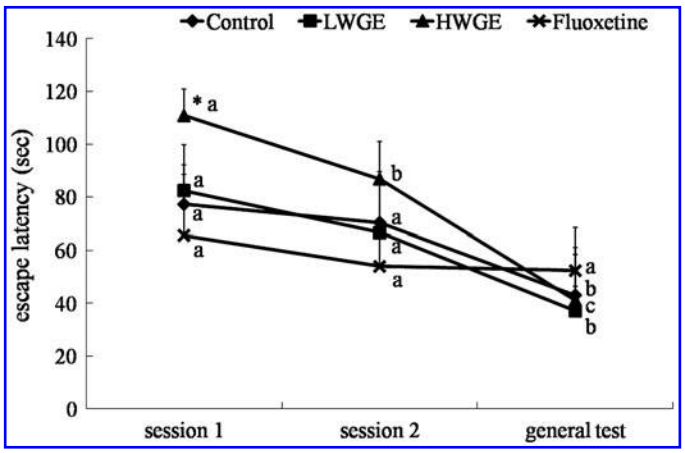

FIG. 6. Effect of *G. elata* Bl. on the escape latency in the Morris water maze of rats experiencing forced swimming before training. Data are mean ± SD values ($n = 8$). All samples were administered for 21 days by oral gavage at the following dosages: Control, 10 mL/kg of body weight deionized water; LWGE, low-dose water extract of *G. elata* Bl. (0.5 g/kg of body weight); HWGE, high-dose water extract of *G. elata* Bl. (1.0 g/kg of body weight); and Fluoxetine, fluoxetine (18 mg/kg of body weight). Data analysis was performed using analysis of variance and Duncan's multiple range test. *Significantly different from the control group ($P < .01$). [abc]Data not sharing the same letter are significantly different from one another in each group ($P < .05$).

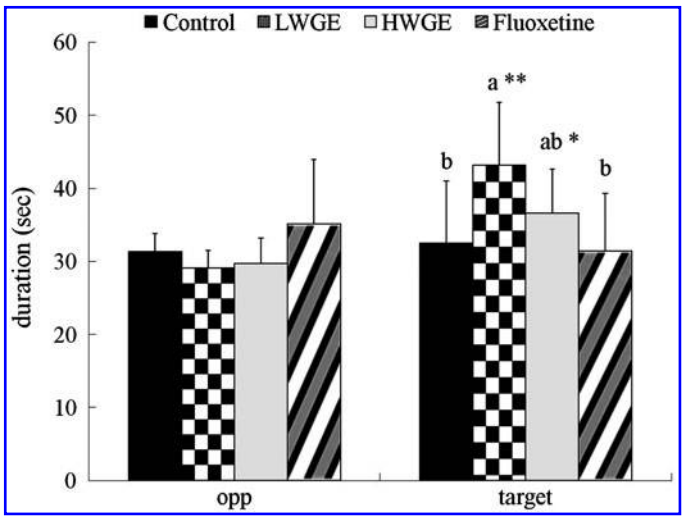

FIG. 7. Effect of *G. elata* Bl. on the duration spent in the target and opposite (opp) quadrants in the Morris water maze of rats experiencing forced swimming before training. Data are mean ± SD values ($n = 9$). All samples were administered for 21 days by oral gavage at the following dosages: Control, 10 mL/kg of body weight deionized water; LWGE, low-dose water extract of *G. elata* Bl. (0.5 g/kg of body weight); HWGE, high-dose water extract of *G. elata* Bl. (1.0 g/kg of body weight); and Fluoxetine, fluoxetine (18 mg/kg of body weight). Data analysis was performed using analysis of variance and Duncan's multiple range test. [ab]Groups not sharing the same letter are significantly different from one another in the duration spent in target zone ($P < .05$); the duration spent in the opp zone is not different among groups. *$P < .05$, **$P < .01$ compared with the duration spent in the opp zone.

tasks. WGE was then administered to test whether it can reverse the adverse effects of depression on learning and memory.

In Experiment 1, forced swimming was introduced at different time points in the training or testing period during the inhibitory avoidance and Morris water maze tasks. This regimen allowed us to determine if effective forced swimming affected the acquisition, memory formation, or memory retrieval of the two learned responses. Pre-training, post-training, and pre-test treatment paradigms probed into the acquisition, consolidation, and retrieval of memory in the two tasks. Results from the inhibitory avoidance task show that in Test 1, acquisition is impaired when rats were subjected to forced swimming before the training session, yet consolidation and retrieval processes were not affected (Test 1). The second test session, held 20 days after the training session, shows an enhancing effect of forced swimming on memory consolidation or retrieval in long-term retention of the inhibitory avoidance response. In the Morris water maze, rats in the pre-training group performed poorer than the control group in the first training session, the first trial of the general test (data not shown), and the probe test. These results reveal that the forced-swimming procedure introduced before a training session significantly impairs rat acquisition of spatial memory in the Morris water maze, but has fewer or no effects on consolidation or retrieval of spatial memory.

Thus, the result in Experiment 1 shows that stress from the forced-swimming procedure impairs rat acquisition ability in both the inhibitory avoidance task and the Morris water maze. As the swimming velocity of rats in the Morris water maze is not significantly different among groups (data not shown) and the two tasks require opposite response styles (not acting or acting) for successful performance and depend upon different motivation, the observed acquisition deficit in the two tasks reflects learning impairment per se rather than sensory or motor impairment or fatigue. Many studies have reported the effects of emotional arousal on learning and memory.[35] This may be due to some stress-increased hormones, such as glucocorticoids, which affect the memory function in animal models and clinical study.[36,37]

Experiment 2 tested effects of WGE on learning deficits induced by the forced-swimming procedure administered before the training session. In the inhibitory avoidance task, both WGE and fluoxetine improve retention performance, and WGE at 0.5 mg/kg of body weight (the LWGE group) shows the best effect. In the Morris water maze, rats in the HWGE group show poor performance, especially in the first training session. The data from both the first test trial of the general test session (data not shown) and the probe test indicate the LWGE group has the best effect on memory improvement. Motor side effects caused by WGE could be ruled out because the locomotor activity of rats is not affected by *G. elata* administration[21] and the swimming velocity in Morris water maze is not significantly different between groups (data not shown). Fluoxetine, a selective serotonin reuptake inhibitor prescribed to treat depression, had memory-improving effects similar to those of HWGE in both tasks.

The mechanism underlying the attenuating effect of WGE on learning and memory deficits induced by forced swimming remains to be determined. Our previous studies found that the antidepressant-like effects of WGE in the forced-swimming test work presumably via monoamine system regulation[22,23] because previous evidence showed that the concentration or metabolism of these neurochemicals is strongly related to depression symptoms.[38–42] Administration of WGE for 21 days significantly increased serotonin content in the HWGE and Fluoxetine groups, as well as the dopamine content in the LWGE, HWGE, and Fluoxetine groups.[23]

While elevation of levels of both serotonin and dopamine may contribute to the antidepressant effects of WGE, concentration changes in these two neurochemicals may exert differential influences on learning and memory.

Previous studies have yielded evidence attesting to a dopamine role in learning and memory. Microinfusion of sulpiride (a D_2 receptor antagonist) into the medial prefrontal cortex attenuates corticosterone-induced impairment in memory retrieval.[43] Activation of dopamine receptors in the basolateral amygdala and nucleus accumbens is related to the memory enhancement.[44,45] D_1 receptors in the anterior medial precentral area[46] as well as the CA1, entorhinal, posterior parietal, and anterior cingulate cortices are also critical in memory formation.[47] By contrast, serotonin infused into the substantia nigra before training[48] or into the posteroventral region after training[49] induces amnesia for rats in the inhibitory avoidance task. Serotonin 5-HT1A receptors in the prefrontal or agranular insular cortex[50] and amygdala[51] and 5-HT2A in the striatum[52] are also involved in acquisition and memory consolidation. Accordingly, the serotonergic activation in specific brain regions may be devastating for memory function, while dopaminergic activation in certain parts of the brain is required for normal memory function. In this study, the memory improvement effect of LWGE in both tasks may be because WGE, at low doses, activates the dopaminergic system somewhere in the brain. However, this beneficial effect of dopaminergic activation appears to be counteracted by the adverse effect of simultaneous serotonergic activation during high doses of HWGE, and thus resulted in an even longer escape latency in the HWGE group than in the control group. Thus, the inverted U dose–response curve of WGE may be related to an interaction between the dopaminergic and serotonergic systems in modulating memory processing at different doses.

CONCLUSIONS

In conclusion, this study demonstrates that learning and memory in rats are impaired by the forced-swimming procedure. WGE significantly attenuates this deficit. The brain regions subserving the WGE effect on learning and memory remain to be elucidated in future research.

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AUTHOR DISCLOSURE STATEMENT

No competing financial interests exist.

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