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GINKO BILOBA EXTRACT (GBE) COULD PREVENT CHRONIC UNPREDICTABLE MILD STRESS INDUCED BEHAVIORALALTERATIONS IN RATS BY FOOD METHOD

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Stress is an everyday burden, endured by most living creatures for all kinds of reasons. The failure of successful adaptation during stressful situations will results in stress-related diseases including depression. In this study, we evaluated the prevention function of GBE by chronic unpredictable mild stress animal model at first time in food method. The results of the sucrose preference test, open-field test and tail suspension test showed that there are significantly difference between GBE treatment group and saline treatment group after Chronic unpredictable mild stress (CUMS). The results indicated that GBE had obvious function on preventing the damage caused by CUMS. GBE can be used as a prevent food on CUMS.

Keywords: CUMS, GBE, Sucrose preference test, Open-field test, Tail suspension test

INTRODUCTION

Stress is an everyday burden, endured by most living creatures for all kinds of reasons. The failure of successful adaptation during stressful situations will results in stress-related diseases including depression. Depression is an incapacitating psychiatric ailment that has been estimated to affect 21% of the world population. According to the World Health Organization, depression is now the fourth most prevalent cause of human disability and will become the second by the year 2020 (Kumar *et al.*, 2011; and Bhatt *et al.*, 2014).

CUMSinduced depression is generally thought to be the most promising and valuable depressive model in animals and has been widely used for investigating the pathophysiology of depression and the associated therapeutic interventions (Willner, 2005; and Mao *et al.*, 2014b). The original, three-week chronic unpredictable severe stress model with diverse severe and unpredictablestressors (electric shocks, immobilization, cold swimming, isolation housing and other strong stimuli) was developed by Katz and coworkers. Then Willner*et al* replaced severe stressors in Katz's model with mild stressors in order to accurately recapitulate the human condition and gained the CUMS model with a variety of mild and unpredictable stressors (e.g., overnight illumination; presence of novel objects; periods of food and/or water deprivation; cage tilt; change of cage mate) (Qiao *et al.*, 2016). CUMS is characterized by a pervasive low mood, loss of interest in usual activities, diminished ability to experience pleasure, withdrawal of interest, felling of worthlessness, and suicidal tendencies. CUMS exposed animal exhibits several neurobehavioral alteration, resembling the symptoms of chronic human depression and widely employed for studying of depression and preclinical screening of antidepressants (Michel *et al.*, 2007; and Bhatt *et al.*, 2014).

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GBE has been used for centuries in traditional Chinese medicine. The main active constituents of GBE are: terpenoids, flavonoids, bioflavonoids, organic acids and polyprenols. The standardized GBE termed "EGb761" consists of 22-27% flavone glycosides, 5-7% terpene lactones (of which 2.8-3.4% consists of ginkgolides A, B, and C, 2.6-3.2% bilobalide), and less than 5 mg/kg (5 ppm) ginkgolic acid (van Beek, 2005; and Kaur *et al.*, 2013). The reported therapeutic efficacy of GBE is likely contributed to the terpenetrilactones (ginkolides and bilobalide) and the flavonoid glycosides (De Feudis, 2003). In this study, the GBE is an ethanolic extract prepared by our lab and contain the same components as EGb-761 with minor difference on content, but the dosage was controlled for food application and kept the GBE function.

Studies have indicated that GBE had numerous functions on memory, anxiety, spatioal learning through different pathways for Neurological diseases (Yamamoto *et al.*, 2007; Ma *et al.*, 2012; and Abd-Elhady *et al.*, 2013). According to these results we predict GBE also has effect on preventing CUMS. In the present study, the CUMS model was used to explore the function of GBE on preventing the animal chronic unpredictable mild stress.

MATERIALS AND METHODS

Animals

Sprague-Dawleyrats weighing 180-220 g were obtained from the Laboratory Animal Research Center of Jiangsu University. All animals were housed in groups on a 12-hour light/dark cycle (lights on at 7:00 AM, lights off at 7:00 PM) under controlled temperature (22±2) °C and humidity (50±10)%, fed with standard diet and water libitum. They were raised one week to adapt environment and test equipment before experiments began. The protocol for the study was reviewed and approved by the Animal Use and Care Committees of Jiangsu University.

The rats were weighed and randomly divided into 3 groups (10/group). The first group animals were Intragastric administration withGBEand made CUMS model at the same timeGBE-CUMS group. The second group animals were Intragastric administration with saline and also made CUMS model at the same timesaline-CUMS group.The last group animals were raised normally as control groupcontrol group. The GBE dosage was 20 mg/kg bodyweight.

Chronic Unpredictable Mild Stress (CUMS)

The CUMS procedure was applied as normal procedurewith a minor modification. Briefly, rats in CUMS adding saline group and CUMS adding GBE group were subjected to one of the following eight kinds of mild stressors in each day: restraint for 1hr, food deprivation for 24 hr, water deprivation for 24hr,cage tilting for 24 hr,damp sawdust bedding for 24 hr, swimming in 4 °C cold water for 5 min, nip tail for 1 min, level shaking for 10 min, noise stimulus ad 11 db for 10 min, and inversion of the light/dark cycle for 24 hr. These stressors were randomly applied for 4 weeks, and each stressor was applied 3-4 times during the whole experiment process. In order to prevent habituation the same stressor could not applied consecutively for 2 days so that the animals could not predict the occurrence of stimulation. CUMS protocol was the same every time to maintain reproducibility and consistency of finding in future. During the stress process, rat was moved into special room to accept the stressor and returned its single cage after accepting the stressor. The control group receiving no stress had free access to food and water.

Sucrose Preference Test (SPT)

The SPT is used to detect the rat sensitivity of the reward by sucrose. Briefly, before the test, rat was trained to adapt to sucrose solution (1%, w/v): two bottles of sucrose solution water were placed in each cage for 24 h and then on bottle of sucrose solution was replaced with water for next 24 h. Followed by deprivation of water and food for 24 h, SPT was conducted at 9:00 in the morning, rat was housed in individual cages and were free access to two bottles containing 100 ml of water and 100 ml of sucrose solution (1%, w/v) respectively. After 3 h exposure, the volumes of sucrose solution and water was calculated as [(sucrose consumption)/(water consumption + sucrose consumption)] × 100. In the test, the bottle was switched to avoid the effect of side preference in drinking behavior.

Open-Field Test (OFT)

The Open-field test was performed by multi conditioning system (TSE Company, Germany). Briefly, the open-field arena was partitioned into 25 equal-size squares, and detected by infrared ray. The test was conducted in a quiet room in the morning. Each rat was placed in the center of the arena and its behavior was recorded for 5 min. Four claws climbing square numbers and rearing time were monitored as an index of locomotors activity and exploratory behavior.

Tail Suspension Test (TST)

The total duration of immobility induced by tail suspension

was measured by tail suspension test equipment (TSE Company, Germany). In this test, a reduction in the duration of immobility is regarded as an indication of antidepressant-like effect. The TST was carried out on the basis of equipment method with a little modification. The rat was isolated and suspended from the tip of the tail approximately 1 cm by adhesive tape, the rat head was isolated to the floor about 35 cm. the whole test process was designed as 5 min. The total duration of immobility was recorded during the final 4 min blinding the treatment groups. Immobility was defined as lack of all movement except for whisker movement and respiration. At last the stop time percent was calculated and for statistics.

Statistical Analysis

Quantitative data were presented as mean±standard deviation (SD). Statistical analysis of data was performed with a one-way ANOVE using Tukey's test for pairwise comparisons of means. Difference was considered statistically significant if the P value was <0.05.

RESULTS

Effect of GBE on the Percentage of SPT

Figure 1 showed the results of sucrose preference test with CMUS. The sucrose preference decreases rapidly when the animal was exposed to chronic unpredictable mild stress both in GBE-CUMS and saline-CUMS group. The difference of GBE-CUMS and saline-CUMS group was significant ($P<0.01$) compared to control group.On the other side, there was also a significant difference ($P<0.01$) between GBE-CUMS group and saline-CUMS group on sucrose consumption. Furthermore, the time point of sucrose preference change is different, the GBE-CUMS group is changed atthe 15 days and the saline-CUMS group is changed at the 22 days. We find that the treatment with GBE canobviously prevent the effect of CUMS.

Effect of GBE on the OFT

We detected the total distance(represent line crossing), center square duration, rearingtimes and total modification times by OFT test, these four parameters evaluate the CUMS extent and the effect of GBE treatment.

Figure 2a showed the results of total walk distance in the whole test. There was no significantly difference of GBE-CUMS group, saline-CUMS group and control group ($P>0.05$). On the other side, there was also no significantly difference between before CUMS and after CUMS ($P>0.1$) by intra-group comparison. These results indicated that CUMS havs no statistical effect of rat total walk distance in the test. Figure 2b showed the results of center square duration in the whole test. We found that after CUMS, GBE-CUMS group and control-CUMS group extended the time resting on the centercompared with before CUMS, on the contrary the saline-CUMS group reduced the time resting on the center. After CUMS, there was significantly difference on GBE-CUMS group and control group compared to the

Figure 1: The Results of SPT with CUMS by Different Substance

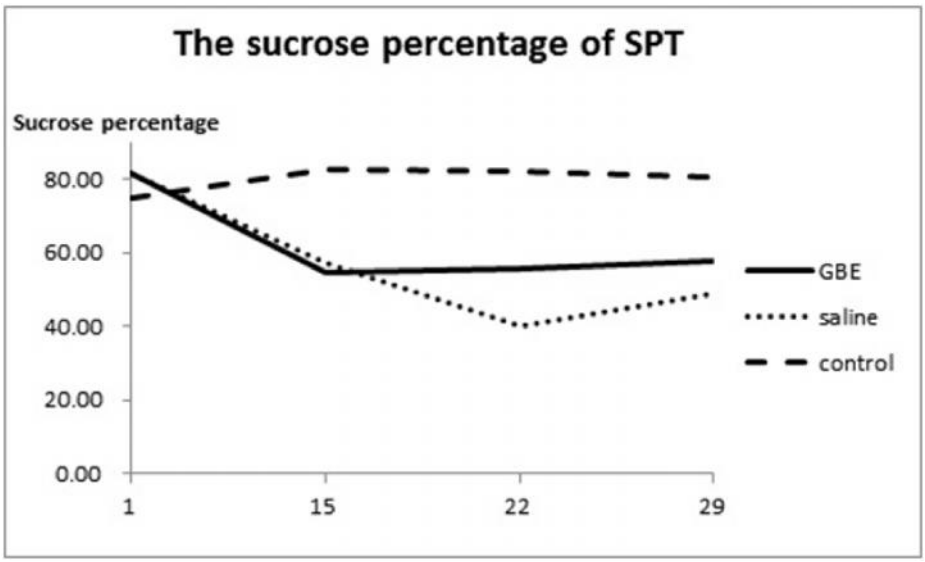
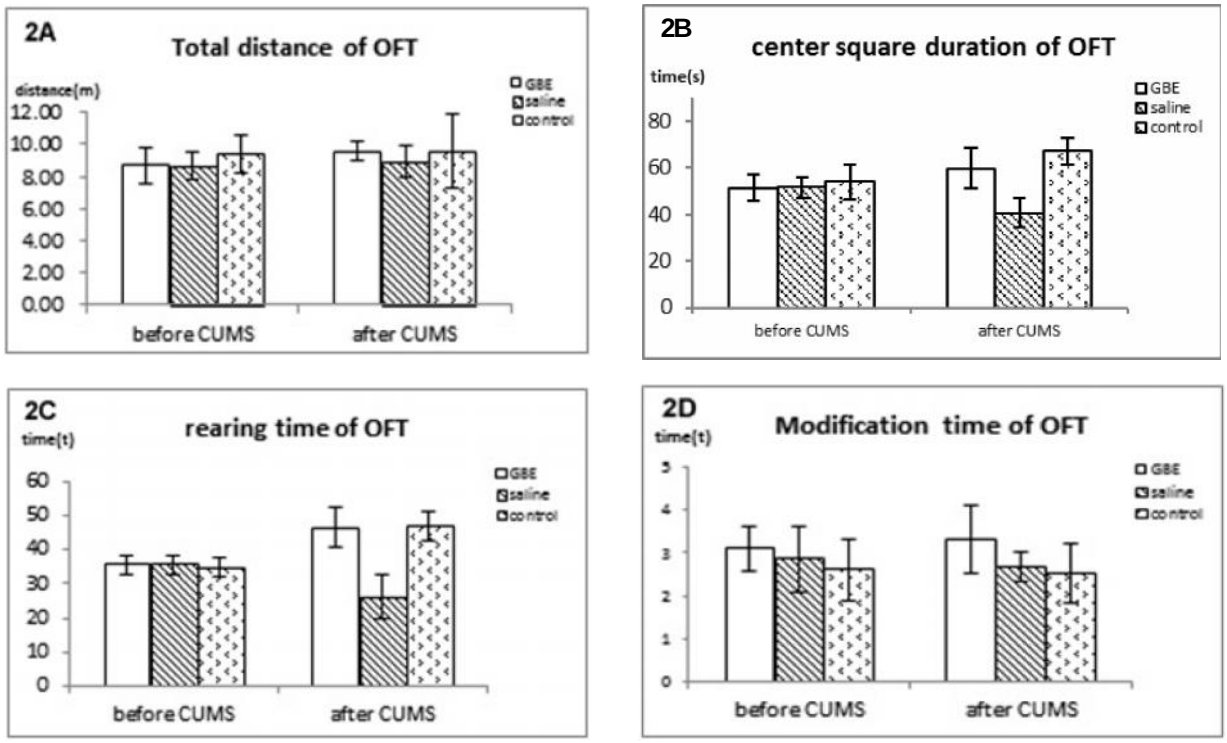


Figure 2: The Results of OFT, (a) The Total Distance Results of OFT, (b) The Time Center Results of OFT, (c) The Stand Time Results of OFT, (d) The Results of Modification Time of OFT



saline group (P<0.01). There was no significantly difference between before CUMS and after CUMS onGBE-CUMS group (P>0.05). On saline-CUMS group there was significantly difference between before CUMS and after CUMS(P<0.01). These results indicated that CUMS can affectcenter square duration, and GBE had protection function for memory damaged by CUMS. Fig. 2C showed the results of rearing times. After CUMS,rearing times of GBE-CUMS group and control group are increased,but the saline-CUMS group is decreased. The GBE- CUMS group and control group had significantly difference comparing to saline group(P<0.01). These results indicated that GBE had well protection on keeping the rat interests to explorer the surrounding. Fig.2D showed the results of modification times of OFT. We could find intuitively from the mean value that the GBE-CUMS group increased the modification times, the saline-CUMS group and control group had a little decrease on modification times. After CUMS, there was a statistical difference between GBE-CUMS group and saline-CUMS group(P<0.05 and P>0.01). These results indicated that the animal of GBE-CUMS had better self-modification capability and lower depression level.

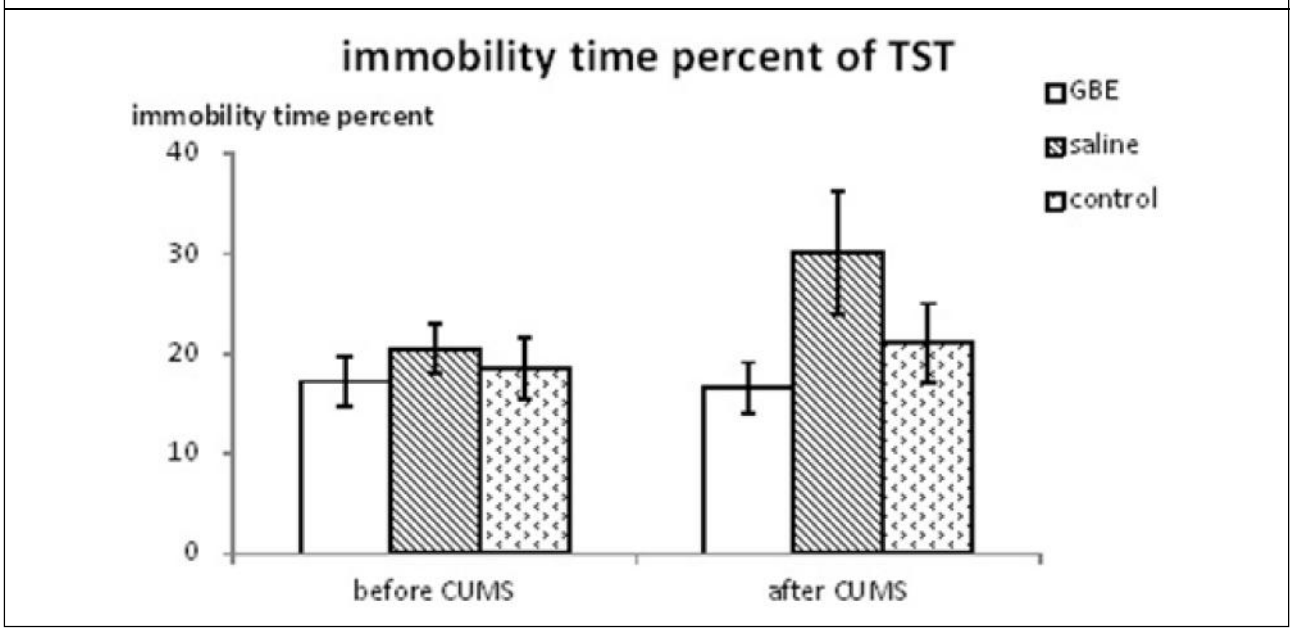
Effect of GBE on the TST

Figure 3 showed the immobility time percent of TST. Generally, CUMS affect rat behavior on TST. After CUMS, animal increased the immobility time percent within 5 minutes, especially saline-CUMS group. The GBE-CUMS group had significantly difference on immobilitypercent compared to saline-CUMS group (P<0.01). The GBE-CUMS group had no significantly change under CUMS between before CUMS and after CUMS. In saline-CUMS group, the immobility time percent increased significantly after CUMS compared to before CUMS (p<0.01). These results indicated that CUMS model reduced the animal active capability and partly behavior desperation,the immobility time increased from 10% to 30%. GBE could keep the animal active capability and prevent the despair status caused by CUMS.

DISCUSSION

The pharmacological treatments for depression currently available include tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin-noradrenergic reuptake inhibitors (SNRIs), and other typical antidepressant drugs such as monoamine

Figure 3: The Immobility Time Percent of TST



oxidase inhibitors (MAOIs) (Kennedy, 2006; Nemeroff, 2007; Kumar *et al.*, 2011; and Yu *et al.*, 2015). However, these antidepressants have only 60-70% effective response rates on patients and long-terms medication always causes significant side effects such as sedation, apathy and fatigue, sleep disturbance, cognitive impairment, sexual dysfunction, etc(Cai et al., 2015; Kennedy, 2006; Sarko, 2000). Hence,to find some food to prevent CUMS still have a pressing requirement. Recently,some study showed that kinds of plants or plants extracts could be used as medicine and food, such as sesamol, fish oil, piperine, campsisgrandiflora flower, resveratrol, which have the active anti-oxidative effect, the active antidepressant-like effect, and the active for preventing depression or CUMS (Kumar *et al.*, 2011; Dexiang Liu *et al.*, 2014; Liu *et al.*, 2014; Mao *et al.*, 2014b; Tang *et al.*, 2015; and Yu *et al.*, 2015). It has been reported that GBE may act by several mechanisms including antioxidant effect, inhibition of platelet activating factor, enhancement of hippocampal neurogenes, protection of the neurons from excito-toxicity, inhibition of glucocorticoid synthesis, scavenging of free radicals, anti-inflammatory activity, and anti-apoptotic activity, especially on neurocognitive effects (Saleem *et al.*, 2008; Ma *et al.*, 2012; Abd-Elhady *et al.*, 2013; and Kaur *et al.*, 2013). In this study, the prevention function of GBE on CUMS was confirmed for the first time by behavior test, and the GBE could be applied in the food production.

Animal models are important tools for studying and understanding kinds of illness, especially in depression. The depression is a kind of specific symptoms of human psychiatric disorders, most of symptoms need to found by mood and behavior (Kumar *et al.*, 2011; Su *et al.*, 2014; and Zhu *et al.*, 2015). CUMS is a well-established animal model for depression. The original, three-week chromic unpredictable severe stress (CUS) model with diverse severe and unpredictable stressors was developed by katz and coworker. In order to accurately recapitulate the human condition, Willner*et al*replaced severe stressors in Katz's model with mild stressors, and augmented the CUMS model with a variety of mild and unpredictable stressors. In willner's model, exposure of animals to 7-13 mild stressors up to 3 months produced a longer lasting depression–like behavior anhedonia (Qiao *et al.*, 2016). The CUMS model of depression is also a well-validated depression model to evaluate the efficacy of antidepressants (Cai *et al.*, 2015; Jiang *et al.*, 2015; and Yu *et al.*, 2015). In this study, it is also the best suitable animal model to evaluate the GBE function.

The sucrose preference test is regarded as useful and valid behavior marker of chronic stress in an animal paradigm. Sucrose preference is also regarded as an indicator of a key symptom of depression, i.e., anhedonia, indicating loss of interest or pleasure (Kumar *et al.*, 2011). In the present study, the results indicated that the sucrose preference decreases rapidly when the animal was exposed to chronic unpredictable mild stress method, suggesting a persistent

reduction in the responses to pleasurable stimuli and revealing a good effect of CUMS animal model. After treatment with GBE about 15 days, the GBE-CUMS treatment group changed the sucrose consumption and sustained a higher level, but the saline-CUMS treatment had no change until 22 days and sustained a lower level on sucrose consumption. Furthermore, treatment with GBE prevented the decrease in the percentage of sucrose consumption of CUMS-treated rats compared with the CUMS-treated rats by saline treatment, the difference is significant ($P<0.01$). OFT and TST are classic method to evaluate the animal behavior for CUMS. Numerous studies have reported that the rodents (mice and rats) exposed to stress exhibit depressive-like behavior evidenced by OFT and TST test (Liu *et al.*, 2014; Mao *et al.*, 2014a; and Filho *et al.*, 2015). Our studies also apply these two methods to detect the CUMS model extent and GBE efficiency. In OFT test, the total animal walk distance, the time center, the stand time and the modification time in whole test process were recorded and analyzed by SPSS. The OFT results showed that the time center, the stand time and the modification time in whole test process preferably display the model efficiency of stressors on CUMS by comparing the difference between before CUMS and after CUMS ($P<0.05$ or $P<0.01$). After CUMS, there was significantly difference on GBE group and control group compared to the saline group ($P<0.01$). In TST test, After CUMS, animal increased the immobility time percent within 5 minutes, especially saline group. There is significantly difference of immobility time percent between GBE-CUMS group and saline-CUMS group ($P<0.01$). All of the results adequately indicated that GBE had better prevent function to CUMS damage.Interestingly, on total walk distance of OFT we also found that there was no significantly difference among three groups ($P>0.05$). On the other side, there was also no difference between before CUMS and after CUMS in statistics ($P>0.1$).These results were not the same as the other studies on depression (Zhang *et al.*, 2014; and Xu *et al.*, 2015). This may be caused by different extent of depression and stressor to animal.

In this study, we confirmed that the GBE in food have prevention function on CUMS damage, but the molecular mechanism under the function is still unknown. 5-hydroxytryptamine (5-HT) system is a key object for lots of experiments and researchers. 5-HT system connected with the central Hypothalamic-Pituitary-Adrenocortical (HPA) axis, including Corticotropin-Releasing Hormone (CRH) and adrenocorticotropic hormone (ACTH), to form a complex regulate system for dealing with all kinds of depress signal (Pang *et al.*, 2014; Wang *et al.*, 2014; and Wu *et al.*, 2014). On the other side, the Brain-Derived Neurotrophic Factor (BDNF), a member of the nerve growth factor family, is certificated that it has important regulatory function on CUMS (Yi *et al.*, 2014; Mao *et al.*, 2014a; and Liu *et al.*, 2015). We will further confirm whether GBE has the same regulatory pathway in the future.

CONCLUSION

In the present study, we confirmed GBE had obvious function on preventing the damage caused by CUMS through SPT, OFT, and TST behavior test in food method.

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