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Extract of sesame cake and sesamol alleviate chronic unpredictable mild stress-induced depressive-like behaviors and memory deficits

Zhigang Liu[1,*], Xiaoning Liu[1], Shunyi Luo, Chuanqi Chu, Dandan Wu, Runhua Liu, Lei Wang, Jiamin Wang, Xuebo Liu[*]

Laboratory of Functional Chemistry and Nutrition of Food, College of Food Science and Engineering, Northwest A&F University, Yangling, China

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ABSTRACT

Depression is a worldwide severe psychiatric disease associated with cognitive impairments. The aims of the present study are to investigate the preventive effects of alcoholic extract of sesame (*Sesamum indicum* L.) cake (SLE) and sesamol in a chronic unpredictable mild stress (CUMS)-induced mouse model. Oral administration of SLE (600 mg/kg/day) and sesamol (10 mg/kg/day) significantly restored CUMS-induced mice antidepressant-like behaviors, anhedonia, and anxiety. Importantly, supplementation of SLE and sesamol inhibited oxidative stress and improved serotonin levels in depressed mice brain. Moreover, SLE and sesamol treatment significantly prevented CUMS-induced memory loss in Y-maze and water-maze tests, which was consistent with enhanced the size of postsynaptic densities and postsynaptic density protein 95 (PSD-95) expression in mice hippocampus. These results illustrated that SLE and sesamol markedly improved CUMS-induced depression and memory loss, and provided novel insights into the mechanisms of sesamol and sesame crude extract on the regulation CUMS-induced depression and cognitive impairments.

1. Introduction

Depression is one of the most severe psychiatric disorders worldwide. Over 10% of the population is suffering from mood, anxiety disorders, and chronic stress. Accumulating evidence suggest that exposure to prolonged stress is associated with memory impairment (Radley et al., 2004). As the core brain structure supporting memory, hippocampus is sensitive to chronic stress (Conrad, 2008). Hippocampal atrophy and dysfunction have been repeatedly documented in depression (Craig A Stockmeier et al., 2004). It has been demonstrated that stress leads to hippocampus synapses morphology changes, reducing neurogenesis, and disturbances in neurotransmission (Stockmeier et al., 2004). Although the underlying pathophysiology of depression has not been clearly defined, preclinical and clinical evidence suggest disturbances in two vital hormones, serotonin (5-HT) and norepinephrine (NE) (Healy, 2015; Kondo, Omri, Han, & Isoda, 2015; Moret & Briley, 2011). 5-HT and NE are also associated with cognitive processes in central nervous system (CNS) (McEntee & Crook, 1991; Roozendaal & Hermans, 2017). The currently available clinical treatments for depression include 5-HT and NE reuptake inhibitors. However, as the inconsistent efficacy and the side effects such as sedation, cognitive impairment, and fatigue, these antidepressants still need to be replaced by new, safe and effective drugs (Kelly, Posternak, & Jonathan, 2008).

Sesame (*Sesamum indicum* L.) has long been regarded as a health food, and sesame oil is highly resistant to oxidative deterioration due to its high content of lignans (Yamashita, Iizuka, Imai, & Namiki, 1995). Sesame oil is also one of traditional herbal drug for pain relief and anti-inflammation in some Asian countries (Shamloo et al., 2015). Sesame cake, a by-product of the oil industry, is currently used as sheep or cattle feed (Fitwi & Tadesse, 2013). The alcoholic extract of sesame cake (SLE) has been well-documented to possess antioxidant activity (Mohdaly, Smetanska, Ramadan, Sarhan, & Mahmoud, 2011; Suja, Jayalekshmy, & Arumughan, 2005). Although the bioactive components of SLE are not fully chemically characterized, the phenolic compounds and lignans including sesamol, sesamin and sesamolin, may play essential roles of its bioactivities (Jeong et al., 2004). For instance, sesamol (SML, 3,4-methylenedioxyphenol), a natural lignan present in the extract, possesses various bioactivities including antioxidantive, lipid lowering, and anti-inflammatory effects (Liu, Qiao, et al., 2017).

Abbreviations: CUMS, chronic unpredictable mild stress; SLE, sesame cake extract; NE, norepinephrine; 5-HT, serotonin; NF-κB, Nuclear factor kappaB; PSDs, postsynaptic densities; MAO, monoamine oxidase; HPA, hypothalamus-pituitary-adrenal; CAT, catalase; MDA, malondialdehyde; GSH, glutathione; BDNF, brain derived neurotrophic factor

* Corresponding authors at: College of Food Science and Engineering, Northwest A&F University, Xinong Road 2, Yangling 712100, China.
E-mail addresses: zhigangliu@nwsuaf.edu.cn (Z. Liu), xueboliu@aliyun.com (X. Liu).

[1] These authors contributed equally.

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Previous of our research demonstrated that sesamol ameliorated systemic inflammation induced memory loss and amyloid-beta accumulation in mice brain (Liu, Chen, Qiao, et al., 2017). It was also found that sesamol improved western diet induced oxidative stress and behavior deficits in CNS (Liu, Sun, et al., 2017). Importantly, sesamol has also been reported to exert antidepressant-like effects in behavioral despair paradigm in chronically stressed mice (Kumar, Kuhad, & Chopra, 2011). However, whether SLE or sesamol could improve depression-related memory deficits are still unclear.

The current study performed experiments with chronic unpredictable mild stress (CUMS) model, the most acceptable chronic stress model for screening antidepressants (Forbes, Stewart, Matthews, & Reid, 1996; Willner, Towell, Sampson, Sophokleous, & Muscat, 1987). Previous research reported that CUMS elicited various diseases, including psychiatric disorders, endocrine disorders, and memory function loss (Liu et al., 2015; Liu, Deng, et al., 2017). This study was aimed at uncovering the effects of dietary sesamol and sesame crude extract supplementation on CUMS induced depression mice model by (a) characterizing the effects of SLE and sesamol on mice anxiety and depression behavioral tests including sucrose preference, tail suspension test, open field test, forced swimming test and elevated plus maze test; (b) examining the effects of SLE and sesamol on cognitive function of CUMS treated mice; (c) uncovering the effects of sesamol and sesame crude extract on endocrine expressions; (d) determining the effects of SLE and sesamol on CUMS-elicited hippocampal synapse morphology alterations. Above all, it provides novel insights into the mechanisms of SLE and sesamol on the regulation CUMS-induced depression and cognitive impairment.

2. Materials and methods

2.1. Chemical and alcoholic extract preparation

Sesamol (98%, S3003) and all other chemicals were the purest grade available from Sigma-Aldrich (St Louis, MO, USA). Dried sesame cake (125 g) were powdered and extracted with 1000 mL of 85% ethanol for 2 h at 50 °C. Cooled to room temperature, the extract was centrifuged at 4000 rpm for 4 min at 4 °C, and the supernatant was concentrated under vacuum at 55 °C to give crude extracts. Then, the extract samples were re-dissolved in distilled water with ultrasonic treatment (100 W). After the completion of dissolution, the crude extract was pre-frozen for 4 h at −80 °C followed by cryodesiccation for 48 h (LGJ-10C freezer drying machine, Four-Ring Science Instrument Plant Beijing, China).

2.2. HPLC and polyphenols content detection

The lignans were detected by HPLC (CBM-20A, Shimadzu, Kyoto, Japan) as described in previous research (Saha, Dinar, Nabila, & Roy, 2014). Separation was carried out on an Agilent ZORBAX SB-C18 column (4.6 × 250 mm, 5 μm) with column temperature 30 °C. The mobile phase consisted of methanol (Tedia Company, Inc., Fairfield, USA) (solvent A) and water (solvent B) with a gradient system: 0–15 min, 45% A; 15–20 min, 85% A; 20–25 min, 85%A; 25–26 min, 45%A. The flow rate was 1.0 mL/min (injection volume 10 μL) with detection at 290 nm. Each sample was repeated thrice, and the average of the three values was counted as the final sesamin, sesamol or sesamolin content.

The analysis of the main polyphenols present in the sesame cake and the lignans, were performed for the diffusion kinetics. Initially, 0.1 g of SLE was dissolved in 10 mL 85% ethanol (10 mg/mL). 100 μL of extract solution and 1000 μL of the Folin-Ciocalteau reagent (diluted 8 folds in distilled water) were mixed and left to react for 5 min. Then, 800 μL of Na_2CO_3 solution (9 g of Na_2CO_3 and 100 g of water) was added. The mixture was kept for 90 min at room temperature. Measurements were performed using a UV–vis spectrophotometer (UVmini-1240, Shimadzu, Kyoto, Japan) at 760 nm. The concentration of total polyphenols was calculated by standard graph values of gallic acid; thus results are expressed as gallic acid equivalents (GAE) per 100 g of dry matter (DM).

2.3. Animal experiments

3 month-old C57BL/6J mice were purchased from Xi'an Jiaotong University (Xi'an, Shanxi, China). Mice were single-housed in the animal facility under standard conditions (12/12 light-dark cycle, humidity at 50 ± 15%, temperature 22 ± 2 °C). All mice were fed with a standard diet (AIN-93M) and assigned to four groups (n = 10/group): Control, CUMS, CUMS + SLE, CUMS + Sesamol. Different groups of animals were oral gavage with vehicle (0.01 mL/g), SLE (600 mg/kg/day, dissolved in saline), and sesamol (10 mg/kg/day), respectively. The behavioral tests were performed 1 h later after drug administration. After all behavior tests, mice were sacrificed. Anesthesia was induced by an i.p. injection of chloral hydrate (Sigma, St. Louis, MO) at a dose of 400 mg/kg in phosphate-buffered saline (PBS). Blood samples were separated from orbital eye bleeding under anesthesia. Brain samples were collected, and the cortex and hippocampus were isolated. All of the experimental procedures followed by Guide for the Care and Use of Laboratory Animals: Eighth Edition, ISBN-10: 0-309-15396-4, and the animal protocol was approved by the animal ethics committee of Northwest A&F University.

2.4. Chronic unpredictable mild stress (CUMS) procedures

The CUMS protocol was adapted from the procedure described as previous research (Liu et al., 2013) (Fig. 1A) and consisted in a variety of stressors applied randomly and at different times of day during 35 days, i.e., S1: 5-min cold swimming (at 4 °C), S2: 1-min tail pinch (1 cm from the tip of the tail), S3: 24-h food and water deprivation, S4: overnight illumination, S5: 15-min force swimming (at 23 °C), S6: 24-h cage tilting (30°), and S7:200 mL of water for sawdust dampness per cage (sufficient to reach the moisture of the sawdust bedding). These stressors were randomly scheduled over a 1-week period and repeated throughout the 5-week experiment.

2.5. Behavior tests

2.5.1. Morris water maze test

A spatial memory test was performed as previously described with minor modifications (Choi et al., 2012). The Morris water maze is a white circular pool (diameter: 150 cm and height: 35 cm) with a featureless inner surface (XR-XM101, Shanghai Xinruan Information Technology Co. Ltd, Shanghai, China). The circular pool was filled with nontoxic water and kept at 23–25 °C. The pool was divided into four quadrants of equal area. A transparent plastic platform (4.5 cm in diameter and 14.5 cm in height) was centered in one of the four quadrants of the pool. There are four prominent visual cues on each side of four quadrants of the pool. The swimming route of mouse, from the start position to the platform, was monitored and analyzed by a video tracking system (SuperMaze software, Shanghai Xinruan Information Technology, Co. Ltd, China). Four habituation training were performed on first day (day 0). The water in the pool was un-dyed, and the platform was visible (1.5 cm above the water surface). Test trials were conducted for 4 days (day 1-day 4). The water was white-dyed with non-toxic agents (Food grade titanium dioxide), and the platform was submerged 0.5–1.0 cm below the water surface so that it was invisible at water level. For each daily trial, the mouse was placed into the water maze at one of three randomly determined locations and released allowing the animal to find the hidden platform. After the mouse found and climbed onto the platform, the trial was stopped and the escape latency was recorded. The maximum trial length was 60 s. If animals did not locate the platform within 60 s, the experimenter guided the