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

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A B S T R A C T

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) ( McIntee & Crook, 1991; Roozenaal & Herrmans, 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 antioxidant, lipid lowering, and anti-inflammatory effects (Liu, Qiao, et al., 2017).

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

The current study performed experiments with chronic un-
predictable mild stress (CUMS) model, the most acceptable chronic
stress model for screening antidepressants (Forbes, Stewart, Matthews,
& Reid, 1996; Willner, Tovell, 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
eextract 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 suspen-
sion 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
sonication (120 W) for 1 h. 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., Fair
field, 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 sesa-
molin 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
Na2CO3 solution (9 g of Na2CO3 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 poly-
phenols 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, Shaanxi, China). Mice were single-housed in the an-
imal facility under standard conditions (12/12 light-dark cycle, hu-
nidity 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 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
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
food and water deprivation, 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 fea-
tureless 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 dia-
meter 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 plat-
form 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 al-
lowing 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
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