Journal of Food Processing & Technology
ISSN: 2157-7110

Pervin et al., J Food Process Technol 2017, 8:10
DOI: 10.4172/2157-7110.1000695

Research Article OMICS International

Improvement in Cognitive Function with Green Soybean Extract May Be Caused by Increased Neuritogenesis and BDNF Expression

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Abstract

Green soybean (*Glycine max* L.), which was used in this study, retains the green color of the seed coat cotyledon even after ripening, even though many soybean cultivars become yellow during maturation. We have reported that ingestion of green soybean extract (GSE) suppressed cognitive dysfunction and reduced amyloid β accumulation more than yellow soybean extract (YSE) in aged senescence-accelerated (SAMP10) mice, a mouse model of brain senescence. To clarify the mechanism by which GSE suppresses cognitive dysfunction, we examined the effect of GSE and YSE on neurite outgrowth in human neuroblastoma SHSY-5Y cells. GSE significantly increased cell number and neurite outgrowth at 5 ng/ml (as isoflavones, 30 pg/ml), but the effect of YSE was lower than that of GSE. Although isoflavone aglycones, genistein and daidzein increased the number of SH-SY5Y cells, the effect was only observed at a high concentration [0.05 μM (13 ng/ml)]. ICR mice were fed a diet containing 3% soybean extract for 3 weeks (3-4 g/kg; as isoflavones, *ca*. 20 mg/kg) to examine cognitive function. Learning and memory abilities, as evaluated by a step-through passive avoidance task, a Y-maze and a novel object recognition test, were significantly higher in mice that ingested GSE than control mice that were fed a normal diet. The expression of brain-derived neurotrophic factor (BDNF) in the hippocampus, as detected by western blot analysis, was higher in mice that ingested GSE than in control mice. This study suggests that the ingestion of GSE enhances learning and memory abilities in mice. The effect by which GSE improved cognitive function appears to be caused, in part, by increased neuritogenesis and BDNF expression.

Keywords: Brain-Derived Neurotrophic Factor (BDNF); Cognitive function; Green Soybean; Neuritogenesis; SH-SY5Y cell

Introduction

Glycine max (L.), commonly known as soybean is a species in the Leguminosae family that is widely used for its edible bean. Soybean is a rich source of proteins, oligosaccharides, dietary fibers, minerals and phytochemicals, particularly isoflavones [1,2]. Numerous beneficial effects of soybean and its components have been reported on cognitive function and oxidative damage [3-7]. Immature soybean seeds are usually green before it is harvested and becomes yellow during maturation. However, the green soybean cultivar that was used in this study retains the green color of their seed coat cotyledons, even after ripening. In the present study, we focused on green soybean and compared the effect on brain function relative to a yellow soybean cultivar. While yellow soybeans, which are the most abundant and have mainly been studied, green soybean extract (GSE) was recently reported to have immune-modulatory and anti-inflammatory effects [8,9]. In addition, we recently reported that the ingestion of GSE ameliorated cognitive dysfunction and amyloid β (Aβ) accumulation in aged senescence-accelerated mice (SAMP10) [10]. SAMP10 mice exhibit a short life span, brain atrophy in the frontal region, neuronal loss and cognitive dysfunction with aging [11-13]. The expression of *Ptgds*, which encodes lipocalin-type prostaglandin D2 synthase, a putative endogenous Aβ-chaperone, was significantly associated with a green soybean diet [10,14]. It has been shown that *Ptgds* is mainly expressed in oligodendrocytes in brain parenchyma [15], and the expression of this gene is regulated by estradiol [16]. Soy isoflavones such as genistein, daidzein and their metabolites, equol, can bind to estrogen receptors (ER α/β) with a comparably higher affinity than 17β-estradiol [17]. We speculated that isoflavones present in GSE might be involved in the activation of *ptgds* expression by binding ER to estrogen response elements thereby improving brain dysfunction. In the present study, in order to clarify the mechanism by which GSE suppresses brain aging, we first examined the effects of GSE and yellow soybean extract (YSE) on SH-SY5Y cells, which have been used to observe neurotrophic activity-inducing neurite outgrowth as well as cell number growth in cell culture system [18,19]. This activity was compared with that of soy isoflavones such as genistein and daidzein. We also examined whether a relatively short period of administration of GSE could alter learning and memory abilities of young mice using a Y-maze, novel-object recognition and a step-through passive avoidance task. In addition, since brain-derived neurotrophic factor (BDNF) is a key mediator involved in both neurogenesis and cognitive function, we examined the expression of BDNF in the hippocampus of mice that ingested GSE.

Materials and Methods

Preparation of soybean extract

Japanese cultivars of green soybean ('Echigomidori') and yellow soybean ('Fukuyutaka') were used. Soybeans (10 g) crushed into a

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Received September 12, 2017; **Accepted** October 02, 2017; **Published** October 09, 2017

Citation: Pervin M, Unno K, Nakayama Y, Ikemoto H, Imai S, et al. (2017) Improvement in Cognitive Function with Green Soybean Extract May Be Caused by Increased Neuritogenesis and BDNF Expression. J Food Process Technol 8: 695. doi: 10.4172/2157-7110.1000695

powder were dispersed with 100 mL of distilled water by stirring at 90°C for 2 h and filtered. The soluble portion was freeze-dried and used as the soybean extract for experiments as described previously [10]. The yield from soy powder was 35%.

Cell growth assay *in vitro*

Human SH-SY5Y neuroblastoma cells (ATCC, CRL-2266) were plated in a 100-mm flask and cultured in D-MEM/Ham's F-12 with L-glutamine, phenol red, HEPES and sodium pyruvate (Wako Pure Chemical Industries Ltd., Osaka, Japan), containing 10% fetal bovine serum (Mediatech Inc., Tokyo, Japan) and a mixture of 1% penicillin-streptomycin (Nacalai Tesque Inc., Kyoto, Japan). The cell culture was incubated at 37°C under 5% CO_2 for 48 h, as described previously [20]. The cells were plated as 1×10^5 cells/mL in a 24-well plate (500 µL of cell suspension/well). Test samples were dissolved in 0.01% DMSO (Wako) were added to the culture medium to make a final concentration of 1 ng-1 µg/ml for GSE and YSE and 0.01-1 µM for daidzein and genistein (Wako) in triplicate for each concentration. Control cells were treated with the DMSO solvent alone. Plates were incubated for 48 h. Cells were counted with a TC10™ Automated Cell Counter (Bio-Rad, CA, USA). The experiment was carried out twice for each test sample.

Quantitation of neurite outgrowth

SH-SY5Y cells were plated as 2.5×10^4 cells/mL in a 24-well plate (500 µL of cell suspension/well). GSE and YSE dissolved in 0.01% DMSO were added to the culture medium to make a final concentration of 5 ng/ml, and cultured for 72 h. Control cells were treated with the DMSO solvent alone. Cells were visualized by phase-contrast microscopy using an inverted microscope (IX71; Olympus, Tokyo, Japan) with a LUCPIanFLN 20x/0.45 objective lens (Olympus). Neurite length was measured by ImageJ software (Ver. 1.50i), as described previously [20]. Assays were performed in triplicate and at least three photos from each culture were taken.

Animals, diets and green/yellow soybean extract

Male ICR (4-week-old) mice were purchased from Japan SLC Co., Ltd. (Shizuoka, Japan) and bred under conventional conditions in a temperature- and humidity-controlled room with a 12-h light/dark cycle. Mice were fed a normal diet (CE-2; Clea Co Ltd., Tokyo, Japan) containing 3% GSE or YSE for 3 weeks (3-4 g/kg). Control mice were given free access to a normal diet and water. All experimental protocols were approved by the University of Shizuoka Laboratory Animal Care Advisory Committee (approval No. 136068) and were in accordance with the guidelines of the US National Institutes of Health for the care and use of laboratory animals.

Memory acquisition test

A step-through passive avoidance task was carried out using ICR mice as described previously [10]. In brief, when a mouse entered the dark chamber from the light chamber, the door was closed and an electric foot-shock was delivered at 50 µA for 1 s (MST-01S; Muromachi Kikai Co., Ltd, Tokyo, Japan). Acquisition of the avoidance response was judged as successful if the mouse remained in the light chamber for 300 s. The trial was repeated until the mouse satisfied the acquisition criterion within five trials. For each trial, the time spent in the light chamber was subtracted from 300 s. This result from successive trials was summed for each mouse to give a measure of the time required for learning ("learning time").

Working memory (Y-maze)

For this test, searching behavior was observed in a Y-maze (MYM-01M; Muromachi Kikai Co., Ltd.). The behavior of each mouse, i.e., the positions of the maze arms it entered and the number of times it entered each arm, was observed for 8 min, as described previously [21]. 'Alternation behavior', i.e., entering the three different arms successively, was considered to reflect working memory capacity.

Novel object recognition test

To evaluate short-term memory of young ICR mice, a novel objective recognition test was performed. The floor of the test box (30 × 40 × 25 cm) was covered with 50 g of wood chips similar to the home cage. Mice, with or without soybean extract fed over 3 weeks, were allowed to explore the box freely in the presence of two identical sample objects for 10 min. After mice were returned to their home cages for 10 min, they were again introduced into the box in which one object was replaced by a novel object. The time to explore each object was determined within 10 min. The ratio of the amount of time spent exploring the novel object was obtained as an index for short-term memory as follows:

Ratio = (time spent exploring novel object) / (total exploring time for both familiar and novel objects).

Measurement of brain weight (cerebral weight)

After the behavioral analyses, mice were sacrificed by bleeding from the carotid and jugular vein under anesthesia. After their brains were removed immediately, the brain was rinsed with ice-cold saline and wiped. After weighing, the brain was separated into two parts: the cerebrum, and the cerebellum containing the pons and medulla. The weights of both mice groups (mice that were given soybean extract and control mice) were compared. The hippocampus was kept at -80°C for western blot analysis.

Western blot analysis

Hippocampal tissues were lysed on ice using RIPA lysis buffer (Wako) containing a protease inhibitor mixture (Sigma-Aldrich, USA). An equal amount of total protein (30 µg) from tissue homogenate was loaded onto a 15% SDS-polyacrylamide gel along with a molecular weight marker (Bio-Rad Laboratories, Inc., USA). Protein bands on the separating gel were transferred to a polyvinylidene difluoride membrane (Immun-Blot® PVDF, 0.02 µm, Bio-Rad Laboratories) according to the manufacturer's instructions. Membranes were blocked for 3 h in blocking buffer (PVDF Blocking Reagent, Can Get Signal®, Toyobo) at room temperature and incubated in solution 1 (Can Get Signal ™, Immunoreaction Enhancer Solution for primary antibody, Toyobo, Tokyo, Japan) with the primary antibody (Anti-rabbit BDNF antibody, Chemicon International Inc., Temecula, CA, USA) overnight at 4°C. Membranes were washed with TBST (Tris-buffered saline with Tween-20) and then incubated in solution 2 (Can Get Signal ™, Immunoreaction Enhancer Solution for secondary antibody) with the secondary antibody (anti-rabbit HRP, Wako) for 1 h at room temperature. Specific bands were detected using a chemiluminescent substrate luminal reagent (GE Healthcare, Tokyo, Japan) and the optical density of bands was scanned and quantified using a chemiluminescence imaging system (Ez-Capture II, ATTO Cooled CCD Camera System, Tokyo, Japan). β-actin was used as the loading control.

Statistical analysis

Data are expressed as the mean ± SEM. Statistical analyses were performed using one-way analysis of variance (ANOVA) followed by Bonferroni's *post hoc* test for multiple comparisons. Differences were considered to be significant at $p<0.05$.

Results

Effect of soybean extract, daidzein and genistein on nerve cell growth

GSE significantly enhanced cell number of SH-SY5Y at 0.005 µg/ml (Figure 1a). The effect was lower in the presence of ≥0.1 µg/ml, indicating that there is an optimal concentration of GSE in cell proliferation. Although YSE also increased cell number at 0.005-0.1 µg/ml, the efficacy was lower than that of GSE (Figure 1b). To examine the effects of soy isoflavone aglycone on nerve cell growth, cells were incubated with daidzein and genistein. Daidzein at 0.05 µM (13 ng/ml) significantly enhanced cell number but the effect was lower in the presence of ≥0.5 µM (Figure 2a). Genistein also significantly increased cell number at 0.05 µM, but the efficacy was lower than that of daidzein (Figure 2b).

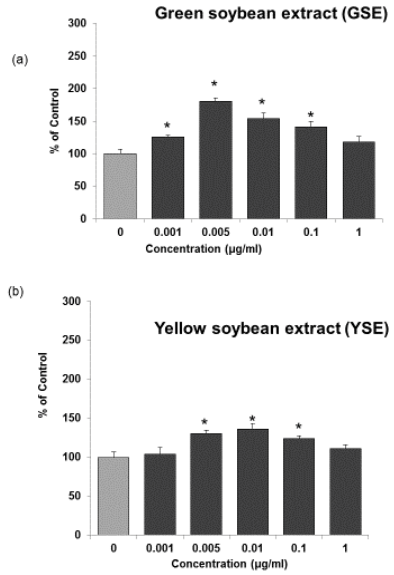

Figure 1: Effect of GSE and YSE on the growth of human SH-SY5Y neuroblastoma cells. [A cell suspension (5 × 10^4 cells/well) was plated in a 24-well plate. Soybean extract dissolved in 0.01% DMSO was added to the culture medium to make a final concentration of 0.001-1.0 µg/ml, and cultured for 48 h at 37°C. The number of cells treated with GSE (a) and YSE (b) are shown. Each value represents the mean ± SEM (n=3). Asterisks represent significant differences (*p<0.05, Bonferroni's t-test)].

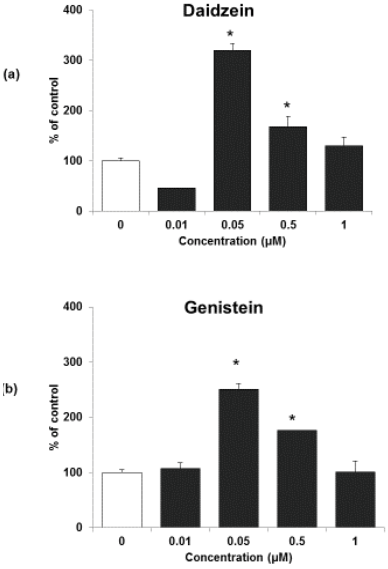

Figure 2: Effect of daidzein and genistein on cell growth of human SH-SY5Y neuroblastoma cells. [A cell suspension (5 × 10^4 cells/well) was plated in a 24-well plate. Daidzein and genistein, which were dissolved in 0.01% DMSO, were added to the culture medium to make a final concentration of 0.001-1.0 µM, and cultured for 48 h at 37°C. The number of cells treated with daidzein (a) and genistein (b) are shown. Each value represents the mean ± SEM (n=3). Asterisks represent significant differences (*p<0.05, Bonferroni's t-test)].

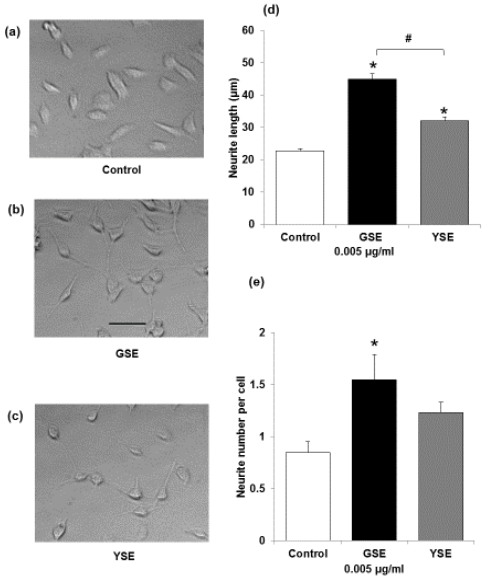

Figure 3: Effect of GSE and YSE on neurite outgrowth of human SH-SY5Y neuroblastoma cells. [A cell suspension (2.5 × 10^4 cells/well) was plated in a 24-well plate. Soybean extracts dissolved in 0.01% DMSO were added to the culture medium to make a final concentration of 5 ng/ml and cultured for 72 h at 37°C. The photos are of control cells (a), or cells treated with GSE (b) or YSE (c). Summarized data of neurite length (d) and neurite number (e) in cells treated with GSE and YSE. Scale bar is 50 µm. Each value represents the mean ± SEM (n=100). Asterisks and # represent significant differences with the control (*) and with yellow soybean (#) (*p<0.05, Bonferroni's t-test)].

Effect of soybean extract on neurite outgrowth

The neuritogenic ability of GSE and YSE on SH-SY5Y cells was compared. The length and number of neurites were significantly higher in cells treated with GSE at 5 ng/ml than in control cells (Figures 3a, 3b and 3d), suggesting that cell differentiation was induced by GSE. When cells were treated with YSE, the neurite length was significantly longer than in control cells but significantly shorter than in GSE treated cells. The numbers of neurite cells were not significantly different than in control and YSE treated cells (Figures 3c, 3d and 3e).

Learning and memory abilities of mice that ingested GSE or YSE

The time for learning not to enter a dark room was measured using a step-through passive avoidance task. A longer learning time indicates lower learning ability. The learning time was significantly shorter in mice that were fed GSE than control and yellow soybean groups (Figure 4a). To investigate working and short-term memories of mice that ingested GSE or YSE, mice were subjected to a Y-maze and made to perform a novel objective recognition test, respectively. The alternation ratio was significantly higher in mice that were fed GSE than in control

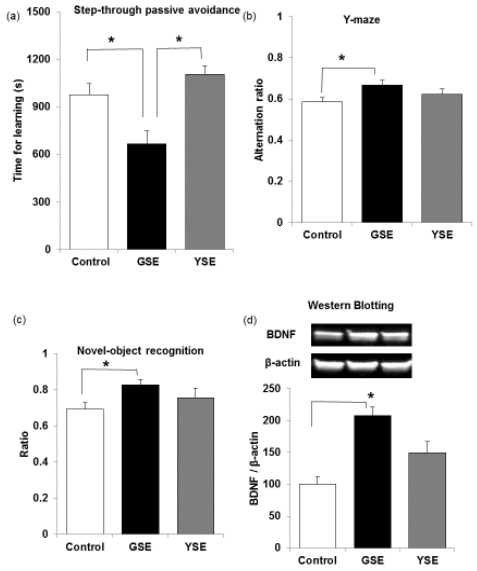

Figure 4: Effect of GSE and YSE on cognitive function in ICR mice. [Learning ability was examined using a step-through passive avoidance task (a). A shorter learning time indicates higher learning ability. Working memory was observed using a Y-maze (b). A higher alternation ratio indicates greater working memory. The novel object recognition test was carried out as an index of short-term memory (c). BDNF expression in the hippocampus was detected by western blot analysis (d). The relative value for BDNF vs β-actin was obtained. Each value represents the mean ± SEM (a-c, n=16-27; d, n=6). Asterisks represent significant differences (*$p < 0.05$, Bonferroni's *t*-test)].

ICR mice (male) (3 months old)	Control (n=10)	Soybean	
		Green (n=10)	Yellow (n=6)
Body weight (g)	43.53 ± 1.11	44.64 ± 1.46	43.76 ± 1.43
Whole brain	0.513 ± 0.007	0.534 ± 0.006*	0.521 ± 0.003
Cerebrum	0.383 ± 0.007	0.401 ± 0.005	0.389 ± 0.003
Cerebellum	0.130 ± 0.001	0.134 ± 0.002	0.133 ± 0.001
*p<0.05, Bonferroni's *t*-test.			

Table 1: Effect of GSE and YSE on brain and body weight.

mice, suggesting that working memory increased in mice following the ingestion of GSE (Figure 4b). The result of the novel object recognition test showed that mice fed GSE spent significantly more time exploring the novel object than the control mice, suggesting that short-term memory was enhanced by the ingestion of GSE (Figure 4c). These results indicate that GSE treatment enhanced cognitive performance in young ICR mice.

Effect of soybean extract on brain and body weights and on BDNF expression in the hippocampus

Feeding mice soybean extract did not change body weight but whole brain weight was significantly higher in mice that were fed GSE than in control mice (Table 1). The level of BDNF in the hippocampus of mice that ingested GSE for 3 weeks increased relative to mice in the control group (Figure 4d).

Discussion

We previously discovered that age-related decline in cognitive function was significantly suppressed in mice that ingested GSE compared to control mice and mice that ingested YSE [10]. Since the high content of isoflavones in green soybean was thought to be an important reason for improved cognitive function [10], we decided to examine the effect of GSE on nerve cell proliferation and differentiation using SH-SY5Y cells. Enhanced neurogenesis in adults is associated with improved learning and memory [22]. The ability to promote neurite outgrowth in neuronal cells *in vitro* is used to evaluate neurogenesis. In this study, cells treated with GSE at 5 ng/ml (as isoflavones, 30 pg/ml) formed significantly longer neurites than control cells (Figure 3). Furthermore, even though genistein and daidzein similarly increased the proliferation of SH-SY5Y cells at 0.05 μM (*ca.* 13 ng/ml) (Figure 2), the effective concentration of isoflavone aglycone (ca. 13 ng/ml) was much higher than the effective concentration of isoflavones in GSE [5 ng/ml (as isoflavones, 30 pg/ml)]. Therefore, isoflavone aglycones may have only a weak effect in neurogenesis. However, isoflavone glycosides that are main component in GSE could potentiate the neuritogenic action.

In the present *in vivo* study, the ingestion of GSE enhanced learning and memory abilities in mice, and these appeared to be, at least in part, related to the up-regulation of BDNF secretion. BDNF is widely expressed in the mammalian brain and is a key mediator involved in both neurogenesis and memory processing [23]. Soybean isoflavones have been found to promote the activity of neurotrophic factors such as BDNF and nerve growth factor in the brain [24-26]. Genistein and daidzein at 0.02-2 μM significantly promoted hippocampus neuronal cell viability and proliferation in the H19-7 neural cell line [27]. These results suggest the importance of isoflavones in GSE.

Since soybean is a rich source of proteins, phytoestrogens, oligosaccharides, and dietary fibers, a combination of these components may exert synergistic effects. In addition, soy peptides, which are generated by hydrolytic enzymatic digestion of soy proteins, may have beneficial effects in preventing cognitive impairment [28,29]. Moreover, these peptides are able to cross the blood–brain barrier [30]. There may be other active components in soybean extract that are involved in improving neuroplasticity other than genistein and daidzein. A further study is needed in which components of GSE are assessed to determine whether they are important for cognitive function.

Conclusion

We found that GSE significantly enhanced the proliferation and differentiation of SH-SY5Y cells and improved learning and memory abilities in young ICR mice. Increased neuritogenesis *in vitro* and increased BDNF in the hippocampus of mice may be involved in improving cognitive function with GSE.

Acknowledgement

This research study was supported by JSPS KAKENHI Grant Number JP23617014 and JP15K00828 and a grant for specially promoted research of the University of Shizuoka.

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