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Ameliorating effects of ethyl acetate fraction from onion (*Allium cepa* L.) flesh and peel in mice following trimethyltin-induced learning and memory impairment

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ABSTRACT

The anti-amnesic effects of onion (*Allium cepa* L.) flesh (OF)[1] and peel (OP)[2] on trimethyltin (TMT)[3]-induced learning and memory dysfunction were investigated to confirm learning and memory function. The inhibitory effect against cellular acetylcholinesterase (AChE)[4] showed that the EtOAc fraction of OP (EOP[5], IC_{50} value = 37.11 μg/mL) was higher than the EtOAc fraction of OF (EOF[6], IC_{50} value = 433.34 μg/mL). The cognitive effects in ICR mice were also evaluated using Y-maze, passive avoidance, and Morris water maze tests. After the behavioral tests, AChE activity (control = 100%, TMT = 128%, EOF 20 = 108%, EOP 10 = 104%, and EOP 20 = 98%), superoxide dismutase (SOD)[7] activity, oxidized glutathione (GSSG)[8]/total glutathione (GSH)[9] and malondialdehyde (MDA)[10] production were examined. These results indicate that both EOF and EOP improved learning and memory function. The main compounds of the EOF and EOP were analyzed by Q-TOF UPLC/MS, and the results were as follows: The EOF (quercetin and quercetin-4′-glucoside) and the EOP (quercetin-4′-glucoside and isorhamnetin-4′-glucoside). Consequently, our results suggest that both EOF and EOP could be efficacious in improving cognitive function through AChE inhibition and antioxidant activity in mice brains.

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1. Introduction

Alzheimer's disease (AD)[11] is a typical age-related neurodegenerative disorder, and is characterized by the progressive loss of cognitive function with an accompanying impairment the ability to carry out daily activities (Choi et al., 2013). In AD patients, the cholinergic function called the "cholinergic hypothesis" was important in the brain for cognition as learning and memory (Bohnen et al., 2005; Terry & Buccafusco, 2003). To date, acetylcholinesterase (AChE) inhibitors (*e.g.* tacrine, donepezil, rivastigmine, and galantamine) have been used as treatments for their ability to increase acetylcholine (ACh)[12] content in the synapses of neurons by inhibiting endogenous levels of AChE and enhancing cholinergic neurotransmission in the brain. However, these agents have reported the burden of side effects (Terry & Buccafusco, 2003). In addition, another role of AChE present in AD brains was found to be associated with neuritic plaques by secretion as a soluble form, may be present with soluble amyloid-β (Aβ)[13], and was associated with free radical oxidative stress and neurotoxicity implications for AD at a very early stage of amyloid plaque formation (Butterfield & Lauderback, 2002; Talesa, 2001). Increased oxidative stress (*e.g.* Aβ, reactive oxygen species (ROS)[14], *etc.*) and increased levels of oxidatively-modified proteins and lipids in the brain of AD patients have also been reported to be a risk factor of AD (Vina, Lloret, Orti, & Alonso, 2004).

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[1] OF: onion flesh.
[2] OP: onion peel.
[3] TMT: trimethyltin.
[4] AChE: acetylcholinesterase.
[5] EOP: EtOAc fraction of onion peel.
[6] EOF: EtOAc fraction of onion flesh.
[7] SOD: superoxide dismutase.
[8] GSSG: oxidized glutathione.
[9] GSH: glutathione.
[10] MDA: malondialdehyde.
[11] AD: Alzheimer's disease.
[12] Ach: acetylcholine.
[13] Aβ: amyloid β.
[14] ROS: reactive oxidative species.

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Trimethyltin (TMT) is a neurotoxin that induces neuronal damage, including the temporal elevation of plasma corticosterone levels, bodyweight loss, and behavioral changes such as whole body tremor (Morita et al., 2006). TMT causes oxidative stress in astrocytes by involving a variety of oxidative species (O_2^-, H_2O_2, NO, *etc.*) (Gunasekar et al., 2001). In addition, TMT causes selective neuronal damage and apoptosis in the dentate gyrus in both the human and rodent hippocampal region (CA1 and CA3 subfields) of their respective central nervous systems (CNS)[15], and induced σ1 receptor dysfunction, which is associated with cholinergic neurotransmission (Shin et al., 2007; Ogita et al., 2005). That is, TMT could induce neuronal damage in the cholinergic systems of animal models, which causes neuronal cell death in the hippocampus (Morita et al., 2006). Therefore, TMT-induced mice were a suitable *in vivo* model for investigating the study of cognitive dysfunction.

The onion (*Allium cepa* L.) is one of the most widely consumed vegetables (Kim & Kim, 2006), and is rich in two chemical groups that have perceived health benefits for humans: Flavonoids and alk(en)yl cysteine sulfoxides (Park, Kim, & Kim, 2007). In particular, onions are a rich source of flavonols such as quercetin 3,4′-*O*-diglucoside and 4′-*O*-glucoside (Bonaccorsi, Caristi, Gargiulli, & Leuzzi, 2008). Onion extracts are also reportedly effective in many other biological activities (*e.g.* antimicrobial, antioxidant, anticarcinogenic, antimutagenic, antiasthmatic, immunomodulatory, prebiotic activity, and cardiovascular disease) (Martinez, Corzo, & Villamiel, 2007). Meanwhile, research into cognitive function was relatively insufficient, and in particular, the learning and memory effect of onion flesh has not yet been reported. Therefore, the beneficial effects of ethyl acetate fraction of onion flesh (EOF) and peel (EOP) on TMT-induced cognition deficits in Institute of Cancer Research (ICR)[16] mice were evaluated and compared.

2. Materials and methods

2.1. Materials

Acetylthiocholine, 5,5-dithio-bis(2-nitro)benzoic acid (DTNB)[17], TMT, thiobarbituric acid (TBA)[18], metaphosphoric acid, dimethylsulphoxide (DMSO)[19], SOD determination kit, and all other chemicals used were purchased from Sigma-Aldrich Chemical Co. (St. Louis, MO, USA). The total glutathione kit was purchased from Enzo life and science (Lausen, Switzerland).

2.2. Sample preparation

Onion (*A. cepa* L.) was prepared from a local market of Changnyeong (Korea), in July, 2013, and was authenticated by Institute of Agriculture & Life Sciences, Gyeongsang National University. A voucher specimen was deposited at the Herbarium of the Department of Agronomy, Gyeongsang National University. Divided into onion flesh (OF) and onion peel (OP) were washed, and lyophilized using a vacuum-tray freeze dryer (IlShin Lab Co., Ltd., Yangju, Korea). Lyophilized samples were ground to a powder, and stored at −20 °C. Powdered OF and OP were respectively extracted with 50-fold volumes of 70% ethanol at 40 °C for 2 h, and were filtered through Whatman No. 2 filter paper (Whatman International Limited, Kent, UK). Extracted OF and OP were consecutively solvent fractionation in a separating funnel using solvents (*n*-hexane, chloroform, ethyl acetate, butanol, and distilled water). The solvents were concentrated using a rotary vacuum evaporator (N-1000; EYELA Co., Tokyo, Japan), lyophilized, and stored at −20 °C. Each sample dissolved 10% DMSO in *in vitro*, and sonicate for 40 min in *in vivo* experiments.

2.3. Inhibition of AChE

The AChE assay was performed according to the colorimetric method of (Ellman, Courtney, Andres, & Featherstone, 1961) using acetylthiocholine iodide as a substrate. For the enzyme source, PC12 cells were homogenized in a Glass-Col homogenizer (Terre Haute, IN, USA) with 5 volumes of a homogenization buffer [10 mM Tris–HCl (pH 7.2), containing 1 M NaCl, 50 mM $MgCl_2$, and 1% Triton X-100], then centrifuged 10,000 ×*g* for 30 min to obtain the supernatant. Sample (10 μL) were mixed with enzymes (10 μL) and incubated at 37 °C for 15 min. Absorbance at 405 nm was read immediately after adding 70 μL Ellman's reaction mixture [0.5 mM acetylthiocholine and 1 mM 5,5′-dithio-bis(2-nitrobenzoic acid) in a 50 mM sodium phosphate buffer (pH 8.0)]. Reading was repeated for 10 min at 2 min intervals to verify that the reaction occurred linearly. Tacrine as a positive control was used in this experiment because of its inhibitory effect of AChE, butyrylcholinesterase (BuChE), and modulating effect of the nicotinic receptor (Aarsland, Mosimann, & McKeith, 2004).

2.4. Animals and in vivo experimental design

All animal experimental procedures were approved at the Institutional Animal Care and Use Committee of Gyeongsang National University (certificate: GNU-131105-M0067), and performed in accordance with the Policy of the Ethical Committee of Ministry of Health and Welfare, Republic of Korea. Institute of cancer research (ICR)[20] mice (male, 4 weeks old) were obtained from Samtako (Osan, Korea). The mice were housed two per cage in a room maintained with a 12 h light & dark cycle, 55% humidity, and 22 ± 2 °C.

The EOF and EOP were orally fed at concentrations of 10 and 20 mg/kg of body weight (designated by EOF 10, EOF 20, EOP 10, and EOP 20, respectively) once a day for 3 weeks. Sample dosage for mice was determined on the basis of previous research (Choi et al., 2012). After 3 weeks, TMT (2.5 mg/kg [7.6 μg/kg of body weight]) was dissolved in 0.85% sodium chloride solution (w/v), and was subcutaneously injected (100 μL) except control group (Choi et al., 2012). TMT group as a negative control means that mouse was only injected with TMT without feeding the any samples.

2.5. Behavioral test

The Y-maze test was performed 3 days after the TMT injection. The maze was black-painted plastic, and each arm of the maze was 33 cm long, 15 cm high, and 10 cm wide, and was positioned at a constant angle. Each mouse was placed at the end of one arm, and allowed to move freely for 8 min. The mouse movement of arm entries was recorded to a smart 3.0 video tracking system (Panlab, Barcelona, Spain), and arm entry have been completed only when the hind foots of the mouse were placed completely. Alternation is defined as entries into the three arms in an overlapping triplet set. The alternation behavior was calculated as the ratio of actual to possible alternation (the total number of arm entries−2), multiplied by 100 (Heo et al., 2004).

The passive avoidance test box was divided into two zones, lighted zone and dark zone. The mice were allowed to move freely through a circular tunnel between the two zones. Each mouse was placed in the lighted zone; as soon as it entered the dark zone, an electric shock was provided (0.5 mA, 3 s). After 24 h, the mouse was again placed in the lighted zone, and the step-through latency time was measured to dark zone (maximum limit time: 300 s) (Heo et al., 2004).

[15] CNS: central nervous systems.
[16] ICR: Institute of Cancer Research.
[17] DTNB: 5,5-dithio-bis(2-nitro)benzoic acid.
[18] TBA: thiobarbituric acid.
[19] DMSO: dimethylsulphoxide.
[20] ICR: institute of cancer research.

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