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Research Article

SOLANUM BETACEUM IMPROVES COGNITIVE FUNCTION BY DECREASING N-METHYL-D-ASPARTATE ON ALZHEIMER RATS MODEL

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ABSTRACT

Objective: The purpose of this study was to evaluate the effect of *Solanum betaceum* towards cognitive function, i.e. memory, and the level of N-Methyl-D-Aspartate receptor (NMDAR) and brain derived neurothropic factor (BDNF) as a drug candidate therapy for Alzheimer rats model.

Methods: Fifty adult male albino rats were divided into five groups (K0, K1, P1, P2 and P3). Four groups (K1, P1, P2 and P3) of Alzheimer's disease (AD) rats were induced by aluminum chloride with dose 2 g/L for 21 days period and three groups (P1, P2 and P3) in 22th day administered parallelly with 100 mg/kg b.w/day; 200 mg/kg b.w/day; and 400 mg/kg b.w/day of *S. betaceum* respectively for14 days. The level of NMDAR and BDNF was measured by enzyme-linked immunosorbent assay methods, whereas memory was measured by the Morris water maze test.

Results: *S. betaceum* administration increased cognitive function significantly (p=0.037) of AD induced-rats by decreasing the time to reach the target of Morris water maze and maintaining the low levels of NMDAR significantly (p=0.006), but the level of BDNF did not increase significantly (p=0.346). These results indicated that ethanol extracts of *S. betaceum* could decrease brain NMDAR and increase cognitive function by promote better memory function but did not significant increased the level of BDNF in AD-induced rats.

Conclusion: This study revealed that the treatment of AD-induced rats with *S. betaceum* extracts significantly improve memory function and decrease the level of NMDAR.

Keywords: *Solanum betaceum*, Memory, N-Methyl-D-Aspartate receptor, Brain-derived neurotrophic factor, Aluminum chloride, Alzheimer.

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INTRODUCTION

Alzheimer's disease (AD), a progressive, irreversible age-related neurodegenerative disease, is characterized by gradually progressive debilitating cognitive decline such as memory loss, disorientation in time and space, difficulty in problems solving, language impairment, psychosocial impairment, behavioral symptoms (hallucinations, paranoia, and delusions), and among others [1-5]. AD is the sixth leading cause of death and a leading cause of dementia among elderly populations of Americans [5]. AD remains a big problem with a significant social, health, and financial burden on society [2]. The latest report infer that AD affects approximately 5 million Americans and 48 million people worldwide (World Health Organization, 2015) and the incidence of AD continuously and rapidly increase with a new diagnosis being made every 68 s [2,6-8]. The population of the world is rapidly aging, so the number of people with dementia is supposed to increase. AD is the most common cause of dementia [2,9].

AD is known as a result from over-production and impaired clearance of β-amyloid [1]. The extracellular amyloid-beta (Aβ) plaques, intracellular neurofibrillary tangles, large scale of neuronal death and neural atrophy, the loss of synapses, changes in neurotransmitter expression, and reduced neutrophil numbers, which all contribute to cognitive decline in a progressive manner, are the main hallmarks of AD [3,10]. Impairment of memory and other cognitive functions in the initial stages of AD are associated with changes in the entorhinal cortex and the hippocampus. Around 80% of the hippocampal neurons may die over the development of the disease, and this progressive loss is manifest in the cognitive impairment and other symptoms seen in patients with AD [3]. Hippocampus is a critical area of neuronal-damaged in AD [7].

Hippocampus, a fundamental role of learning and memory, represents the primary region of adulthood neurogenesis and exerts the largest potential for brain neuroplasticity [11]. Brain-derived neurotrophic factor (BDNF) is one of the fundamental neurotrophic factor in learning and memory, particularly expressed ubiquitous in the brain and playing a key regulator role of development, cognition and plasticity of the hippocampus [9,11-15]. BDNF, a synaptic plasticity marker, is important for long-term potentiation (LTP) like mediating the regulation of excitatory synapses during early LTP [13,16]. BDNF is secreted at pre- or postsynaptic areas. Synaptic BDNF is secreted in response to activity and can activate pre- and/or post-synaptic TrkB receptors. BDNF increases the exocytosis of glutamate-containing synaptic vesicles presynaptically, whereas postsynaptically BDNF–TrkB signaling induces N-Methyl-D-aspartate receptor (NMDAR) phosphorylation [13]. BDNF and NMDA play key role of synaptic plasticity in the hippocampus [13].

Until now pharmacologic management trying to treat AD is only partial inhibitors rather than curative [10]. AD still a big health problem due to lack of efficacy and adequacy of current treatments [5]. Fundamental strategy to combat AD is understanding about the underlying neurobiological processes of cognitive decline [17]. Nutrition may be taken into account play an important role to postpone or prevent the development of the disease. There is strong evidence supporting the importance of nutrition in the prevention and management of AD [10]. A classic feature of AD is dysfunction of hippocampal synaptic plasticity thus modification of synaptic plasticity would be beneficial for memory improvement in AD [7]. *Solanum betaceum* is promising sources of antioxidants due to their high anthocyanins (ACN) content and associated with beneficial effects of health due to anti-inflammatory effects and improved cognitive behavior [18]. Therefore, the current

study aimed to determine whether cognitive impairment of AD, neuroplasticity in the hippocampus can be prevented or improved by *S. betaceum* by checking the BDNF and NMDA levels.

METHODS

Setting

This study has been conducted in the Animal Research Laboratory of Medical Biochemistry Department Universitas Airlangga, Surabaya city, East Java Province, Indonesia.

Chemicals and reagents

The level of NMDA and BDNF was obtained using mybiosource.com, California, Sandiego USA, with Cat No.MBS269995 and Cat No. MBS261374, respectively. Aluminum chloride (ACl_3) has used Cat No.8.01081.0500, MERCK, USA. All of other chemicals and reagents were used of reagent grade and highest purity. Fresh red *S. betaceum* was purchased from local Orchard in Wonosobo, Central Java, Indonesia, identified by Indonesian Institute of Science and processed immediately on arriving at the laboratory.

Animals

Fifty male, 3 months albino rats with an average weight of ±150–180 g were used for this study. The animals were acclimatized to the laboratory conditions for 7 days, allowed free access to food and water *ad libitum*, and maintained under 12 h light and dark cycles at room temperature.

Grouping and experimental design

The animals were randomly divided into five groups (n=10) as follows:

- Group K_0: Negative control
- Group K_1: Aluminum chloride ($AlCl_3$)
- Group P_1: $AlCl_3$ and ethanol extract of *S. betaceum* 100 mg/BW
- Group P_2: $AlCl_3$ and ethanol extract of *S. betaceum* 200 mg/kgBW
- Group P_3: $AlCl_3$ and ethanol extract of *S. betaceum* 400 mg/kgBW.

3 g/L (3 mg/mL) of the stock solution of $AlCl_3$ was used in this study. Duration of $AlCl_3$ administration was 21 days. 1st until 21th days, the rats were given $AlCl_3$ and followed by administration of *S. betaceum* in the 22nd until 36th days. This study was carried out in accordance with the guidelines Ethical Clearance provided by the Animal Care and Use Committee, Faculty of Medicine, Universitas Airlangga with certificate No.259/EC/KEPK/FKUA/2018.

Preparation of *S. betaceum* ethanol extract

Fresh red *S. betaceum* (Tamarillo) fruits were dried by fresh dryer. Dry powder was extracted by maceration using ethanol solvent for 3 h×24 h 3 times at room temperature, then separated between filtrate and residue. The ethanol extract was filtered and evaporated with a rotary vacuum evaporator to obtain a viscous extract. The ethanol extract of *S. betaceum* was added to the treatment diet in as a suspension form with aquadest. During the experiment, the extract of *S. betaceum* was simultaneously administered into the treatment group before $AlCl_3$ exposure.

Consolidation training and memory test (Morris water maze)

The Morris water maze, a water-filled of the round pool, is a well-established apparatus to evaluate hippocampal-dependent spatial learning and memory in rats [17,19]. Rats were trained with extra-maze visual cues (a colorful poster, a traffic cone, and two black-and-white construction paper designs) which are placed around the pool. An escape platform was hidden 1 cm just beneath the surface of the water (Morris, 1984). Most protocols used four start locations: North, South, East, and West. Animals were given a series of daily trials using a random or semi-random set of start locations. Semi-random start position sets were most common, such the four positions were used, with the restriction that one trial each day was from each of the four positions. The rats were gently lowered that the tail-first into the pool with maximum swim time was set to 60 s. If the mouse located the platform before 60 s had passed, it was immediately removed from the pool, whereas if more than 60 s of swimming, the mouse was gently guided to the platform and allowed to re-orient to the distal visual cues with 20 s additional time before being removed from the pool. The memory test was performed with no symbol marks used. The frequency of reaching targets and settling time in the area was recorded and calculated [19]. The value of memory test, as the time required for the rat to reach the target, was expressed in second. The less time to reach the target is indicated good memory of the rats.

Determining level of NMDA and BDNF

Samples were collected from the left or right hippocampus and analyzed using the enzyme-linked immunosorbent assay (ELISA) method. The fixed hippocampus was homogenized using a sonicator added by buffer lysis and then centrifuged at 15,000 rpm for 15 min at 4°C. The supernatant was used to be analyzed. Samples were immediately stored at −20°C. The level of NMDA and BDNF in the hippocampus was determined using the ELISA test.

Statistical analysis

The statistical analysis was performed by one-way ANOVA and Kruskal–Wallis test. The statistical significance between the experimental groups was assessed by least significant difference and Mann–Whitney U-test with $p<0.05$. Data analysis was used by SPSS ver.23.

RESULTS AND DISCUSSION

Table 1 summarized about mean, standard deviation, ANOVA test of NMDAR and BDNF of control and treatment group. ANOVA test revealed NMDAR levels between group differs significantly with p=0.006

Table 1: Mean, standard deviation, ANOVA test of NMDAR, BDNF of rats control and experiment group

Variable	Group[#]					SI	ANOVA
	K_0	K_1	P_1	P_2	P_3		
NMDAR	3.74±1.12[a]	5.73±0.6[b]	3.91±0.19[a]	4.27±0.56[a]	4.30±0.98[a]	ng/ml	0.006*
BDNF	56.18±11.122[a]	36.04±6.83[b]	53.51±2.41[a, b]	50.54±6.57[a, b]	49.24±11.82[a, b]	ng/ml	0.280

*Significantly with $p<0.05$, [#]mean±SD, [a,b]different superscript means significant between groups. NMDAR: N-Methyl-D-Aspartate receptor, BDNF: Brain-derived neurotropic factor, SD: Standard deviation

Table 2: Mean, median, minimum, maximum, and of memory test by Morris water maze test of rats control and treatment group

Variable	Category	Group					SI	Kruskal–Wallis
		K_0	K_1	P_1	P_2	P_3		
Memory/escape latency	Mean	10.71[a]	35.71[b]	15.85[a]	15.57[a]	16.71[a]	Second	0.038*
	Median	11	27	13	8	16		
	Minimum	3	20	4	3	3		
	Maximum	21	83	50	33	51		

*Significantly with $p<0.05$, [a,b]different superscript means significant between groups

($p<0.05$). BDNF count between group did not differs significantly with $p=0.280$ ($p>0.05$).

Table 2 summarized mean, median, minimum, maximum and of memory test of rats control and treatment group. The distribution of memory test from K_0 to P_3 is abnormal, thus used Kruskal–Wallis statistic and revealed differs significantly with $p=0.038$ ($p<0.05$). *S. betaceum* in a dose of 100 mg/kg b.w. was the best dose rather than 200 mg/kg b.w. or 400 mg/kg b.w. for improving memory impairment in AD induced-rats as shown by Morris water maze test.

Administration of *S. betaceum* for group P_1, P_2, and P_3 rats showed a significant increase with $p=0.006$ ($p<0.05$) in their level of NMDAR (Table 1) and decrease time in memory or escape latency test compared to Group K_1 rats which shows the protective effect of memory loss by *S. betaceum*.

It was well established that AD has been related to debilitating cognitive decline and the most common form of dementia with symptoms such as memory loss, disorientation in time, and space, difficulty solving problems, and among others [5,4]. In this study, we have chosen the fresh *S. betaceum* fruits to evaluate its ameliorative effect against AD. This study was aimed to determine the beneficial effect of *S. betaceum* administration on cognitive function, i.e. memory of AD-rats by determining the value of NMDAR and BDNF levels of the hippocampal brain. Male, 3 months albino rats were used as an animal model in this study due to its translationally appropriate and reproducible model to investigate age-related changes to neural systems and cognition [17].

S. betaceum (Tamarillo) fruits, previously known as *Cyphomandra betaceae*, are native and exotic fruits of subtropical and high tropical areas like Indonesia. The commonly used of other names are "tomate de palo," tree tomato, and "tomate de árbol." This fruits belongs to the *Solanaceae* family and *Solanum* genus (Bohs, 1995) [18,20-22]. *S. betaceum* has known as ovoid- or egg-shaped fruits with a glossy, thin and various color of the skin such as reddish-brown, purple-red, golden yellow, and orange-red to cream-yellow. *S. betaceum* has orange pulp, dark red seed with sour and bland taste. The pigment of *S. betaceum* has been published, such as carotenoids and ACN [20,23,24]. *S. betaceum* has divided into two until four types which are distinguished according to their skin colour: Purple-red (often divided into purple and red) and yellow (often divided into amber and gold). The main difference of *S. betaceum* between the yellow cultivars and purple-red cultivars can be seen in the anthocyanin content, which is greatly higher in the purple-red cultivars [22]. Our study has used red *S. betaceum* to be given into AD-rat models.

Red *S. betaceum* is containing rich anthocyanin [22]. Recently, ACN have shown its beneficial effect in memory function. Dietary anthocyanin may positively impact cognitive function and may exert beneficial effect for the prevention and treatment of dementia. Study before, which was conducted by Kent *et al.*, 2015, provided evidence that anthocyanin-rich cherry juice consumption improves memory and cognition in older adults with mild-to-moderate dementia. This study was a randomized controlled trial, assessed cognitive outcomes in 49 older adults (70 years old) with mild-to-moderate dementia after consumption of 200 mL/day of anthocyanin-cherry juice within 12 weeks [25]. Hippocampal-dependent spatial learning and memory can be evaluated using a well-established apparatus called by The Morris water maze. Our observations on Morris water maze test, showed significant differences between control, AD-model and protective group's rats suggest that oral administration of *S. betaceum* might improve memory impairment and behavioral changes in AD-rat models. The results of our study derive strong support from the previous study that consumption of anthocyanin showed significant improvement in memory and cognitive impairment [25].

Neurobiochemical, it has been known that excessive amounts of Aβ peptide in the brain, particularly Aβ42, are responsible as underlying pathology for AD. There are various of potential links between Aβ with the NMDA and NMDAR such as NMDA may be a down-stream target of Aβ, meaning that Aβ mediates the function of NMDAR, the signal of NMDA may influence the assembly of Aβ plaques, NMDAR may bind Aβ through direct or indirect interactions and may mediate Aβ activity relative to plasticity and/or synaptic transmission. The pathogenesis of AD is highly linked with alterations in glutamate signaling, and the tissues affected by AD contain high densities of glutamatergic neurons. Chronic and moderate activation of NMDA receptors result in excitotoxicity and leading to neurodegeneration. This hypothesis of excitotoxicity is supported by clinical evidence indicating that the NMDAR antagonist memantine slows AD progression. Prolonged Ca2+ elevation suppresses synaptic function, leading to subsequent synaptotoxicity and eventually atrophies; these events correlate with the loss of learning and memory functions in AD. Multiple neurotrophic factors have been demonstrated to enhance defense against excitotoxicity [3]. One of the fundamental neurotrophic factors in learning and memory is BDNF [13]. BDNF played a pivotal regulatory role in the regulation of hippocampal structure, development, maintenance, growth, neuronal survival, differentiation, axon growth, formation of neurons, dendritic remodeling, synaptic transmission and modulation, neurotransmitter release, promotion synaptic growth and plasticity of the hippocampus, and cognition [9,11,13-15]. NMDAR and BDNF of hippocampus play a pivotal role of synaptic plasticity in the hippocampus [13]. Rao *et al.* observed that the expression of BDNF in AD brains is decreased and NMDAR-medicated excitotoxicity play a key role in the development of AD [16]. The results of our study showed that in memory- impaired AD-rats induced by $AlCl_3$, *S. betaceum* administration decrease the level of NMDAR significantly with $p=0.006$ ($p<0.05$), but did not change the level of BDNF with $p=0.280$ ($p>0.05$).

Limitation

Limitation of the present study is designed only for behavioral, BDNF, and NMDAR by ELISA aspects involved in the AD. The remaining parameters, including various biochemical changes, morphometric, cholinergic, histological aspects, and gene expression studies, should be performed.

CONCLUSION

Overall, treatment of cognitive impairments in AD-induced rats with *S. betaceum* extract showed its potential in improving effect in memory function as showed in the decreasing time to reach the target of Morris water maze test and decreasing of NMDAR levels of the hippocampal rats. This study strongly indicated that extracts of *S. betaceum* fruits could be good natural sources to improve memory function significantly by a different mechanism of action, such as decreasing the level of NMDAR, but not by changing the level of BDNF, in AD-induced rats. Therefore, consumption of *S. betaceum* in daily dietary intake is a one-step action toward the prevention of cognitive impairments in AD management principle. Further studies are needed to search another parameter involved in memory function of AD-induced rat models.

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CONFLICTS OF INTEREST

The authors declare that all of the authors have no conflicts of interest.

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PAGE 1

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PAGE 3

PAGE 4