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The Efficacy of *Sauropus androgynus* Leaves Extract To Improve Cognitive Function in Wistar Rats Induced Alzheimer's

Rachmat Hidayat[1] , Raden Ayu Adelia Safitri [2], Tungki Pratama Umar [2], Arindi Maretzka[2]

[1]Biology Department, Faculty of Medicine, Sriwijaya University
[2]Undergraduate Student, Faculty of Medicine, Sriwijaya University

 # Correspondence email : dr.rachmat.hidayat@gmail.com

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Abstract

Background

Sauropus androgynus leaves is the substance which has the potency to prevent degenerative processes. Sauropus androgynus leaves has flavonoid as the main component. Flavonoid has antioxidant and anti neuro-inflammation that can be used to prevent Alzheimer dementia. Research purpose is knowing the effect of Sauropus androgynus leaves for the cognitive function and β-amyloid expression in the hippocampus of wistar rats.

Methods

Reseacrh was done by in vivo method, where male wistar rats (n=24) were distributed to six groups which consisting of four rats. Group 1: Normal control, group 2: positive control, group 3: standard treatment (B12 vitamin), group 4, 5 and 6 were give Sauropus androgynus leaves extract with the dose of 75 mg/kgBB, 150 mg/kgBB and 300 mg/kgBB, respectively for 28 days. Cognitive function was evaluated by t-maze test, where hippocampal β-amyloid expression was tested by immunohistochemistry.

Results

Time differences (day 0-28), alternation ratio distinction (day 0-28) and β-amiloid expression were: group 1 (1,84 second; 0,23 unit; 0,518%), group 2 (56,78 second; -0,42 unit; 40,036%), group 3 (34,46 second; -0,25 unit; 33,08%), group 4 (32,83 second; -0,09 unit; 28,88%), group 5 (-3,91 second; 0,42 unit; 14,728%), group 6 (24,25 second; 0,42 unit; 9,4%).

Conclusion

Sauropus androgynus leaves extract at the dose of 150 mg/kgBB and 300 mg/kgBB can maintain cognitive function by decreasing hippocampal β-amyloid formation.

Keywords: *Sauropus androgynus leaves, β-amyloid, t-maze test, flavonoid, cognitive.*

Background

Alzheimer's dementia is one of the most common neurological disorders and occurs in 46 million people worldwide. In Indonesia, the estimated prevalence of the disease reaches 1.033.000 patients in 2015. Alzheimer's disease is becoming one of main discussion because to day, the symptoms of it is happening in productive group of age.[1,2]

Alzheimer's disease is still becoming a concern in the research because its treatment is only symptomatic without any available treatment leading to its etiology. Various research has led to the use of herbal ingredients with various antioxidant compounds, one of them is flavonoids. Natural ingredient that has the potential to face the etiology of Alzheimer's is *Sauropus androgynus* which is considered as having high antioxidant content. Its main flavonoid in the form of kaempferol has good activity as neuroprotective function so it has potential as Alzheimer's prevention method by blocking neuroinflammation.[3,4]

METHODS

This is an in vivo experimental studies. Wistar white rats aged 3-4 months weighing 300-400 grams obtained from the Eureka, Palembang, Indonesia with the approval by Research Ethics Committee of the Faculty of Medicine Sriwijaya University, Palembang, Indonesia. Wistar white rats were placed in different cages with standard feeding and water *ad libitum*. Rats were acclimatized for 7 days in a cage with alternating light and dark cycle settlement at a temperature of about 22^{O}C and about 50-60% humidity.

Sauropus androgynus leaf simplicia was obtained from Indonesian Center for Research and Development of Medicinal and Traditional Medicinal Plants (B2P2TOOT) Tawangmangu, Karanganyar, Central Java, Indonesia. *Sauropus androgynus* leaf was extracted by maceration, where simplicia was mixed with 96% ethanol (Merck®) at a ratio of 1:10 and soaked for 72 hours while stirred every 24 hours. Macerate is then filtered using filtration paper. The obtained filtrate was collected and concentrated with rotary vacuum evaporator and evaporated over a waterbath ± 60 ° C until a constant weight was obtained. The results were weighed on a pot that has been scaled with an analytical scale and stored in a special container. The extract was then tested to assess the content of flavonoids, phenols, alkaloids, steroids and tannins.

This study used 24 male wistar rats which were divided into six treatment groups with each group contained four mice. The inducing agent, $AlCl_3$ (Merck®) was dissolved in aquades before being used. Group 1 was given aquadest orally (normal group) for 28 days. Group 2 was given aquadest and 34 mg/ kgBW $AlCl_3$ orally for 28 days. Group 3 was given vitamin B12 and 34 mg/kgBW $AlCl_3$ orally for 28 days. Group 4 was given 75 mg/kgBW *Sauropus androgynus* leaves extract and 34 mg/ kgBW $AlCl_3$ orally for 28 days. Group 5 was given 150 mg/kgBW *Sauropus androgynus* leaves extract and 34 mg/ kgBW $AlCl_3$ orally for 28 days. Group 6 was given 300 mg/kgBW *Sauropus androgynus* leaves extract and 34 mg/ kgBW $AlCl_3$ orally for 28 days.

This test is done on *t-maze* apparatus at the size of 70x35x12 cm to measure memory and visuospatial abilities of Wistar white rats and is performed three times, i.e. before induction (day 0), 14 days and 28 days after induction. This test is carried out by spontaneous alternation method. The initial phase is carried out with the use of partition and the start arm is closed with a guillotine door. Rats are then allowed to select the desired target, where there is no reward in the goal arm, associated with the natural instincts of rats that tend to choose one side based on their preference. After the mouse

selects one target arm, the guillotine door is closed and the rat is allowed to study the arm for 30 seconds before returning to the initial arm while cleaning the maze. The next stage is the mice are allowed to select the target arm back for the observed behavior which is expected to select the unelected arm (alternation). The experiment was repeated 7 times. The time and direction of the selected arm were noted and compared between the groups.

The rats were first euthanized with chloroform (Merck®) administration before being rapidly decapitated. Surgery then performed on the head of a mouse sagitally to take brain tissue in the hippocampus region. The samples were then fixated using Neutral Buffer Formalin (NBF) solution (Laeca®) and placed in a 4 mm paraffin block. Pieces of the region containing hippocampal and cortical tissue were processed for immunohistochemical staining. After the sample was deparaffinized and rehydrated, the antigen was reactivated by the heat-induced antigen retrieval. Furthermore, slides are given inhibitors at room temperature to inactivate endogenous peroxidase enzymes. Then the slides were incubated with Aβ42 (Cloud Clone®) antibody and diluted to the block solution at a ratio of 1: 100 at room temperature and then stored at 4^{O}C overnight. After being left overnight, Excell Link (Biogear®) was given to the blocking solution for 90 minutes at room temperature. Washing process is repeated and the slides were incubated with Excell HRP (Biogear®) in a blocking solution for 45 minutes at room temperature. The slides were then counterstained with hematoxylin (Biogear®) and followed by 1% lithium carbonate (Biogear®), then examined under a microscope. In addition to testing the micrograph, the expression of Aβ42 are assesed using ImageJ® software.

Data of time difference, alternation ratio difference and β-amyloid expression were analyzed using the IBM® Statistical Package for the Social Sciences (SPSS®) software version 25. The Kruskal Wallis test was performed to compare the average difference due to the number of groups of more than two and the abnormal data distribution. After that, a post-test was performed using the Mann-Whitney U test to determine exactly which groups had significant differences. The value of significance is set at $p < 0.05$.

RESULTS

In this study, it was examined that flavonoid and steroids is the most abundant substance in our *Sauropus androgynus* extract. We also discovered that phenol are present extract in a low level. Meanwhile, tannins, terpennoids and alkaloids were found to be absent in it.

Table 1. Preliminary phytochemical analysis of *Sauropus androgynus* leaves

Test	Results
Flavonoids	+++
Steroids	+++
Tannins	-
Terpenoids	-
Alkaloid	-
Phenolic compounds	+

Table 2. Average time to select T-maze goal arm

No.	Group	Time for Selecting T-maze Goal (second) ± Standard Deviation		
		Day 0	Day 14	Day 28
1	Normal	10,61±9,52	14,12±15,84	12,45 ± 15,98
2	Aquadest + $AlCl_3$	11,55 ± 10,50	25,70 ± 28,09	68,33 ± 82,78
3	B12 vitamin + $AlCl_3$	6,60 ± 5,03	90,31 ± 128,47	41,06 ± 44,50
4	75 mg/kgBW extract + $AlCl_3$	13,15 ± 7,01	66,24 ± 68,14	45,98 ± 43,88
5	150 mg/kgBW extract + $AlCl_3$	8,91 ± 10,44	67,73 ± 84,51	5,7 ± 5,25
6	300 mg/kgBW extract + $AlCl_3$	13,54 ± 8,82	60,55 ± 79,98	37,79 ± 51,82

Table 3. Statistical analysis for mean differences of time in selecting t-maze arm between day 0 and day 28.

No.	Comparison group	Test group	P_value (*)	P_value (**)
1	Normal	Aquadest + $AlCl_3$	0,001	0,005
		B12 vitamin + $AlCl_3$		0,001
		75 mg/kgBW extract + $AlCl_3$		0,034
		150 mg/kgBW extract + $AlCl_3$		0,480
		300 mg/kgBW extract + $AlCl_3$		0,239
2	Aquades t+ $AlCl_3$	Vitamin B12 + $AlCl_3$		0,963
		75 mg/kgBW extract + $AlCl_3$		0,358
		150 mg/kgBW extract + $AlCl_3$		0,005
		300 mg/kgBW extract + $AlCl_3$		0,215
3.	B12 vitamin+ $AlCl_3$	75 mg/kgBW extract + $AlCl_3$		0,783
		150 mg/kgBW extract + $AlCl_3$		0,001
		300 mg/kgBW extract + $AlCl_3$		0,141
4.	75 mg/kgBW extract + $AlCl_3$	150 mg/kgBW extract + $AlCl_3$		0,024
		300 mg/kgBW extract + $AlCl_3$		0,408
5.	150 mg/kgBW extract + $AlCl_3$	300 mg/kgBW extract + $AlCl_3$		0,183

P< 0,05.* Kruskal Wallis. ** Mann Whitney

The results of average time differences between day 0 and day 28 in *t-maze* time and its analysis, are shown in table 2 and 3. The time differences between normal group compared to the group of *Sauropus androgynus* extract at the dose of 150 mg/kgBW and 300 mg/kgBW has no statistical significance. In contrast, negative control group, positive control group and *Sauropus androgynus* extract at the dose of 75 mg/kgBW demonstrate a significant statistical difference. The examination of negative control group of rat (oral administration of $AlCl_3$) and positive control (B12 vitamin) shows significant difference in the mean time differences compared to *Sauropus androgynus* extract at the dose of 150 mg/kgBW.

Table 4. Average alternation ratio of T-maze test.

No.	Group	Average alternation ratio of T-Maze Test		
		Day 0	Day 14	Day 28
1	Normal	0,44	0,61	0,67
2	Aquadest + $AlCl_3$	0,75	0,5	0,33
3	B12 vitamin + $AlCl_3$	0,75	0,39	0,5
4	75 mg/kgBW extract + $AlCl_3$	0,67	0,67	0,58
5	150 mg/kgBW extract + $AlCl_3$	0,41	0,46	0,83
6	300 mg/kgBW extract + $AlCl_3$	0,33	0,46	0,75

Table 5. Statistical analysis for differences of alternation ratio between day 0 and day 28. (*)p_value Kruskal Wallis (**) p_value Mann Whitney, p value is significant at the level of <0,05

No.	Comparison group	Test group	P_value (*)	P_value
1	Normal	Aquadest + $AlCl_3$	0,017	0,025
		B12 vitamin + $AlCl_3$		0,076
		75 mg/kgBW extract + $AlCl_3$		0,286
		150 mg/kgBW extract + $AlCl_3$		0,473
		300 mg/kgBW extract + $AlCl_3$		0,473
2	Aquades t+ $AlCl_3$	Vitamin B12 + $AlCl_3$		0,479
		75 mg/kgBW extract + $AlCl_3$		0,288
		150 mg/kgBW extract + $AlCl_3$		0,009
		300 mg/kgBW extract + $AlCl_3$		0,009
3.	B12 vitamin+ $AlCl_3$	75 mg/kgBW extract + $AlCl_3$		0,613
		150 mg/kgBW extract + $AlCl_3$		0,022
		300 mg/kgBW extract + $AlCl_3$		0,022
4.	75 mg/kgBW extract + $AlCl_3$	150 mg/kgBW extract + $AlCl_3$		0,114
		300 mg/kgBW extract + $AlCl_3$		0,118
5.	150 mg/kgBW extract + $AlCl_3$	300 mg/kgBW extract + $AlCl_3$		1,000

P<0,05. *Kruskal Wallis.**Mann Whitney

The examination of alternation ratio of t-maze test and statistical analysis can be seen on table 4 and 5, respectively. There are significant differences between negative control (aquades + $AlCl_3$) and positive control (B12 vitamin + $AlCl_3$) compared to treatment group (*Sauropus androgynus* extract at the dose of 150 mg/kgBW and 300 mg/kgBW). Concurrently, the examination of normal group did not considered as having significant differences with treatment group (150 mg/kgBW and 300 mg/kgBW extract). Conversely, normal group show significant differences opposed to negative control, positive control and treatment group at the dose of 75 mg/kgBW.

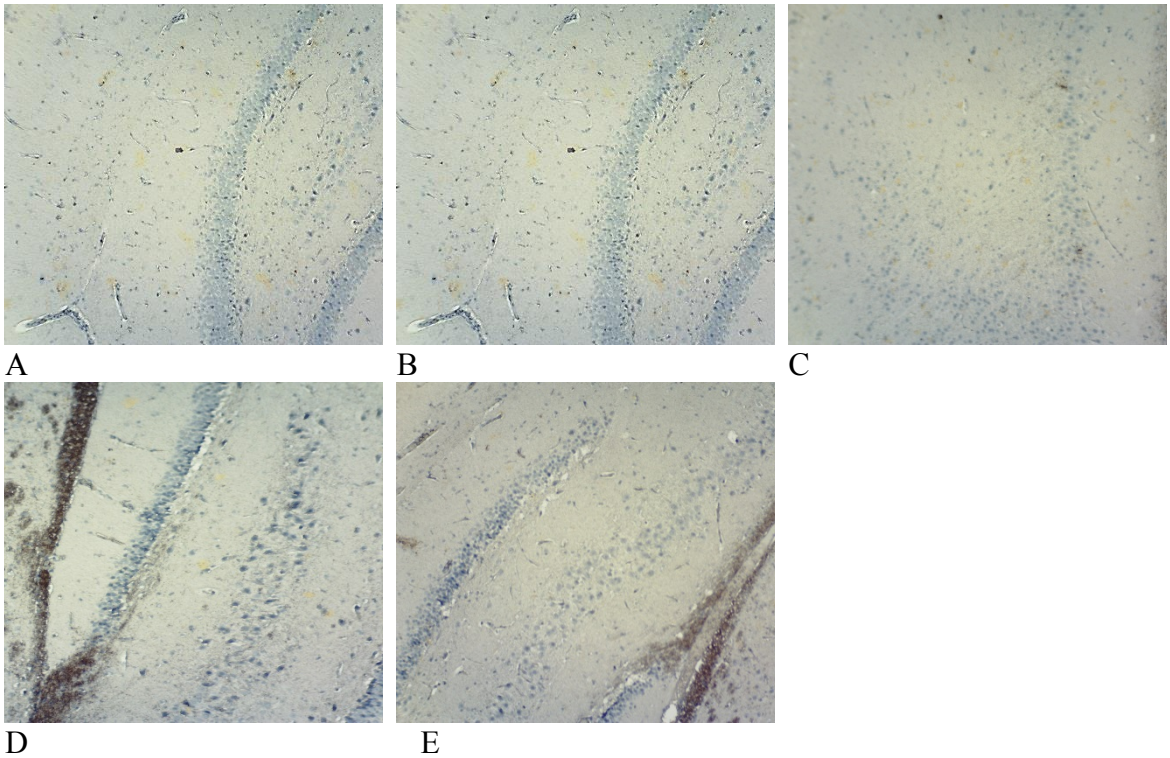

Figure 1. Microscopic appearance of rat hippocampal at the CA1 region. (a) Normal group, (b) negative control, (c) positive control (d) Treatment group: 75 mg/kgBW extract, (e) Treatment group: 150 mg/kgBW extract, (f) Treatment group: 75 mg/kgBW extract

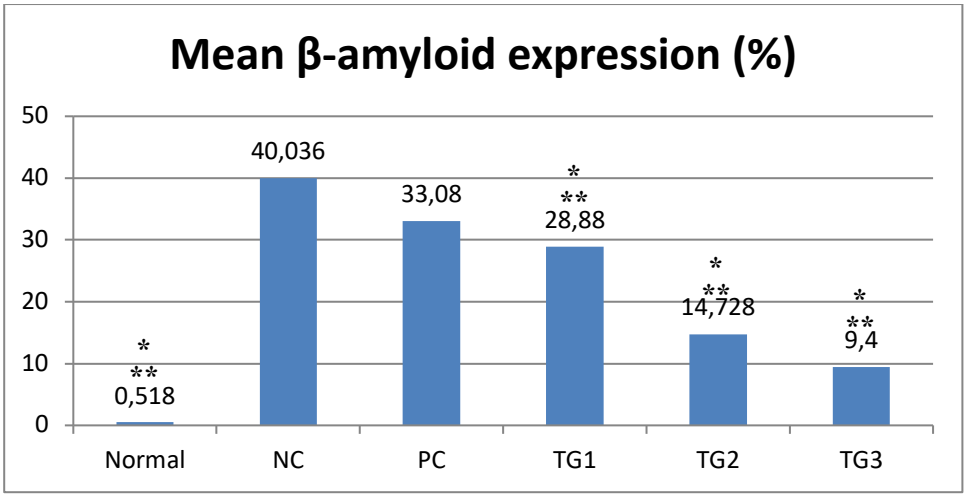

Figure 2. Mean β-amyloid expression of rat hippocampus. NC: Negative control, PC: Positive control, TG1: 75 mg/kgBW extract, TG2: 150 mg/kgBW extract, TG3: 300 mg/kgBW extract. * p<0,05 compared with negative control, ** p<0,05 compared with positive control

Figure 2 showed decreasing neuronal density and excess β-amyloid deposit in negative (aquadest + $AlCl_3$) and positive control (B12 vitamin + $AlCl_3$), compared to normal and the treatment group which is receiving 150 mg/kgBW and 300 mg/kgBW *Sauropus androgynus* leaves extract in hippocampus, especially in the CA1 region (p=0,009; p=0,009; p=0,009, respectively). Reducing neuronal density of pyramidal neuron can be seen by increasing ratio of death cell as presented on photomicrograph in figure 1.

Discussion

In this study, we conducted Alzheimer's disease induction in rats by using aluminium chloride ($AlCl_3$). Aluminium atom (Al) is responsible for free radical formation that can mimic Alzheimer disease development (Falode et al., 2017). Long term administration of $AlCl_3$ is also accountable to disrupt many enzymatic activity, including ones that is related with acetylcholine neurotransmitter, inhibiting calcium ion (Ca^{2+}) channel and interfere synaptic transmission.[5-7]

Besides neurodegenerative processes, $AlCl_3$ is also responsible for neuroinflammatory processes that is associated with memory and learning deficit. Hippocampus, a region that is abundant of pro-inflammatory cytokine receptor, such as for Interleukin-1b (IL-1b), Interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) is vulnerable to inflammation and injury. Proinflammatory cytokine can disrupt long term potentiation (LTP) and inhibiting neurotrophin that has important role in maintaining neuron function and survival, sinaptic plasticity and memory formation.[8] Neurotrophin deficiency, like *Brain-derived Neurotrophic Factor* (BDNF) and *Nerve Growth Factor* (NGF) could cause neurotoxicity due to excess formation of Beta-Amyloid (A*β)* (Peng et al., 2009). A*β* is able to bind four aluminium atoms, increasing the content of β-sheet and increase the severity of neurotoxicity.[9] Aluminium is also an inhibitor of kinase c protein that can

induce Amyloid Precusrsor Protein (APP) by β-secretase which is directed to β-amyloid plaque formation.[10]

Our experiment use *Sauropus androgynus* extract to prevent Alzheimer that is induced by $AlCl_3$. As seen on the result, our extract has flavonoid and steroid as the main content that could avert neurodegenerative and neuroinflammation by Al administration.

Flavonoid in *Sauropus androgynus* extract has neuroprotection and neurogenetic role.[11-13] Flavonoid can infiltrate blood brain barrier (BBB) and is able to scavenge free radical with many mechanism. One mechanism is by absorbing free radical and blocking the formation of *Reactive Oxygen Species* (ROS). Flavonoid is also able to reduce proinflammatory cytokine, β-amyloid plaque production and increasing cell sensitivity to insulin which has positive effect of memory and learning function through the activation of MAPK and PI3 cascade.[14-16] Main flavonoid of *Sauropus androgynus* leaves, kaempferol, has antioxidant activity by means of becoming hydroxil and peroxynitrit radical scavenger, inhibiting enzymatic activity that could regenerate ROS, ameliorating expression or activity of antioxidant enzyme and preventing lipid peroxidation.[17-19] Another flavonoid, quercetin, is able to circumvented neuroinflammation by acting as ROS (such as O_2^-) and RNS (*Reactive Nitrogen Species*), such as NO and ONOO *scavenger*.[20] Quercetin also has inhibitory effect against excessive COX-2 and *inducible nitric oxide synthase* (iNOS) expression that is induced by astrocyte and microglia activation, suppressing uncontrolled β-catenin expression and hinder Wnt pathway (neuroinflammatory regulator) in conjunction with protecting neuron from Aβ-42 toxicity that could restrict apoptosis.[17,18]

Plant sterol has neuroprotective activity. Steroid compound such as diosgenin is able to increase NGF secretion besides becoming reductor for NO production and significantly increase neuronal growth (Woo et al., 2014). Another plant steroid, spicatoside has ability to regulate NGF and BDNF secretion from TrkA receptor-mediated PI3-kinase and ERK1/2 activation pathway as well as cyclic adenosine monophosphate (cAMP) response element binding (CREB) in maintaining neuron function, LTP and preventing neuronal death to halt neurodegenerative processes.[16-18] Prosapogenin is another steroid which has different neuroprotective mechanism, which is by inhibiting macrophage activation by the blockage of MAPK/NF-κB pathway that can lead to the suppression of proinflammatory mediator, such as inducible nitric oxide (iNOS), nitric oxide (NO), cyclooxygenase-2 (COX-2), interleukin-1β (IL-1β) and IL-6.[21] Phystosterol, in the form of stigmasterol can reduce β-amyloid accumulation by deterioraring β-secretase activity, diminishing γ-secretase expression, reducing APP cleavage by its action on cholesterol and BACE1.[22]

Based on the cognitive function results (time and alternation ratio), we can see that there are positive effect of *Sauropus androgynus* extract to the performance of working and spatial memory in addition to exploratory behavior in spontaneous alternation t-maze test. This test is reliable to detect brain abnormality, especially in the hippocampus. Good results from cognitive function can be related to immunohistochemistry imaging. From immunohistochemistry imaging, we can see that there are increasing rasio of apoptotic

pyramidal region in hippocampus, where neuron quantity, in conjuction with dendritic spines and synaptic activity is the determinant of brain functional capacity. Beta-amyloid (Aβ) is one of the main pathological factor in Alzheimer dementia. Excessive Aβ can lead to intricated sequence of neuronal actions and reactions, creating atypical excitatory neural activity and compensatory inhibitory responses associated with learning and memory circuitry especially in neocortex and hippocampus.[15-19] Neuron condition and Aβ has relationship with the performance on t-maze test in every group. According to our observation, *Sauropus androgynus* extract neuroprotective effect has increasing effectivity with higher doses (dose-dependent pattern).

Conclusion

Sauropus androgynus leaves extract at the dose of 150 mg/kgBW and 300 mg/kgBW could increase cognitive function and reduce β-amiloid plaque formation in hippocampal region of the brain.

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