

Supplementation of Water Extract of Purple Sweet Potato (*Ipomoeo Batatas L*) in Improving the EEG Image, Decreasing the Seizure Frequency and Reducing the Frequency of Drugs Resistant of Focal Epilepsy in Children

I. Gusti Ngurah Made Suwarba¹, Soetjningsih¹, I. Made Bakta²,
I. Made Jawi³, I. Dewa Made Sukrama³, I. Wayan Putu Sutirta Yasa⁴
and Irawan Mangunatmadja⁵

¹Department of Child Health, Faculty of Medicine,
Udayana University-Sanglah Hospital, Bali-Indonesia.

²Department of Internal Medicine, Faculty of Medicine,
Udayana University-Sanglah Hospital, Bali-Indonesia.

³Department of Pharmacology, Faculty of Medicine,
Udayana University-Sanglah Hospital, Bali-Indonesia.

⁴Department of Clinical Pathology, Faculty of Medicine,
Udayana University-Sanglah Hospital, Bali-Indonesia.

⁵Department of NeuroPediatric, Faculty of Medicine,
University of Indonesia-RSCM Hospital, Jakarta-Indonesia.

*Corresponding author E-mail: suwarbangurah@yahoo.co.id

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The water extract of purple sweet potato contains of anthocyanin, a sub-class of flavonoid that has powerful antioxidant, antiinflammatory, and anticonvulsant effect. The aim of this study was to determine the effectiveness of supplementation of water extract of purple sweet potato towards recovery (remission) of drug resistant focal epilepsy (DRFE) in children with standard conventional antiepileptic medicine. It was found that the supplementation of purple sweet potato extract had a pure effect in improving all of the dependent variables, including decreased of the serum level of 8-OHdG by 1.611 pg/mL ($p < 0.001$); decreased the serum level of IL-6 by 3.320 pg/mL ($p < 0.001$); increased the total SOD serum level by 0.208 IU/mL ($p = 0.003$); improved the EEG image ($p = 0.004$); and decreased the seizure frequency at the end of the sixth week by 3.972 times ($p < 0.001$), compared to the control. There is a significant effect on the use of supplementation of purple sweet potato extract in decreasing the serum level of 8-OHdG, decreasing the serum level of IL-6, increasing the total SOD serum level, improving the EEG image, decreasing the seizure frequency at the end of the sixth week, which at the end reducing the frequency of drugs resistant of focal epilepsy in children.

Keywords: Children; DRFE; Epilepsy; Purple Sweet Potato; Seizure.

Epilepsy is one of the main problems in the field of neuropaediatric that require long-term treatment of two to three years or even a lifetime. Treatment with antiepileptic drugs (AED) achieved

remission (“cured”) of about 60-70%, while the non-pharmacological treatment is not satisfactory, so that 30-40% of cases happened to be drug-resistant epilepsy (DRE).¹ Anti-epileptic drugs

are symptomatic, only suppress seizure activity but can not affect or improve the pathogenesis and progression. DRE has a very serious impact on development, quality of life and mortality.^{2,4}

DRE is a failure to use = two kinds of AED which are tolerant and appropriately selected and used in accordance with the schedule, either monotherapy or in combination to achieve seizure-free phase.^{1,2} DRE could happen through different patho-mechanism and have not entirely understood.³ Several hypotheses tried to explain these problems, such as: "the target hypothesis" stated that the AED failure to give effect due to a decreased sensitivity of targeted receptors caused by several things including oxidative stress and inflammation.^{3,4}

Studies in the last decades have found that there is a relationship between seizures with oxidative stress, in which oxidative stress play a role in the initiation and progression of seizures in epilepsy. Oxidative stress occurs not only as a result of a seizure, but instead oxidative stress causes damage and death of nerve cells in the brain so as to actively contribute to the occurrence of recurrent seizures and epileptogenesis.^{4,5}

Signs of chronic inflammation and excessive expression of inflammatory mediators and cytokines such as Interleukin-1 β (IL-1 β), Interleukin-6 (IL-6), and tumor necrotizing factor (TNF) has been found in patients with DRE.⁵ Inflammatory process in the brain causing neuron hyperexcitability and seizures. In opposite, seizures cause increased production of such cytokines that aggravate seizures and the onset of recurrent seizures. So there is a reciprocal relationship between seizures, oxidative stress, and inflammation.^{6,7,8}

Purple sweet potato (*Ipomoea batatas* L / Balinese purple sweet potato/sela bojog) is a local plant in Bali. The water extract of purple sweet potato contains of many anthocyanin, a sub-class of flavonoid that has powerful antioxidant, anti inflammatory and anticonvulsants effect.^{9,10,11} Study on animal had a lot to prove this problem, but clinical study is very limited, especially in children.

There is still no publication about research on the use of anthocyanin in children with DRFE with a large number of subjects. Researchers aim to know the effectiveness of supplementation of water extract of purple sweet potato towards remission

of DRFE children with standard antiepileptic conventional medicine compared than the placebo.

MATERIAL AND METHODS

This study used a randomized pre-test and post-test control group design. Children with DRFE aged 1-5 years who met the inclusion criteria and exclusion criteria were selected and included in the study. The inclusion criteria include: 1) All DRFE children aged 1-5 years, male and female diagnosed according to the 2009 International League Against Epilepsy (ILAE) criteria, 2) Children with DRFE new and old cases diagnosed within a maximum period of 6 months from the time it was used as the research subject, 3) Willing to take part in the study as evidenced by the parent / guardian's informed consent. Exclusion criteria include: 1) children with epilepsy syndrome, 2) Children with cerebral palsy, 3) DRFE patients who receive = 3 AED, 4) Active CNS infection: meningitis, encephalitis, meningoencephalitis, brain abscess, 5) Real congenital abnormalities in the brain between others: meningocele, encephalomeningokel, porensesfali, anencefali, congenital hydrocephalus, and hidranensesfali, 6) Suffering from systemic diseases such as pneumonia, dengue haemorrhagic fever, severe dehydration diarrhea, heart failure, acute kidney failure and chronic kidney failure, 7) Malignant diseases such as leukemia, lymphoma, Hodgkin's disease, brain malignancy, lung malignancy, kidney malignancy. Samples were stated to drop out during the course of the following: 1) Disobedient drinking standard AED and / or purple sweet potato tuber extract, 2) Experiencing severe or serious allergies to standard AED and / or extract of purple sweet potato tuber, 3) Experiencing serious illness according to exclusion criteria, 4) Resigning from the study for certain reasons.

Subjects were grouped randomly into two treatment groups and control groups. Randomization is done by simple stratified random sampling. The treatment group received a standard extract of purple sweet potato and AED (carbamazepine and valproic acid) and the control group received standard AED with starch syrup (carbamazepine and valproic acid), each for six weeks. Researchers and subjects did not know whether the subjects included treatment or control

groups before the study ended. Before and after the study, the two groups were examined for serum levels of 8-OHdG, IL-6, SOD, EEG and seizure frequency per two weeks, then the results were compared between the two groups.

The research was carried out in Pediatric Department of Medicine Faculty of Udayana University at Sanglah Hospital. At the end of the study, data analysis was carried out to see the effect of supplementary therapy of purple sweet potato tuber extract on serum levels of 8-OHdG, IL-6, SOD, improvement in EEG image and decrease in seizure frequency per 2 weeks compared to controls. If the number of subjects drops out = 10%, is not included in the data analysis (on treatment analysis) or does the intention to treat analysis if the drop out is > 10%.

RESULTS

This study was conducted at Sanglah Hospital for 12 months from June 2015 until May 2016, obtained 91 subjects that met the inclusion criteria, however, 15 subjects were eventually

excluded, thus 76 subjects satisfy the overall study criteria. During the study period, four subjects dropped out, thus leaving 72 subjects for analysis.

Study Sample Characteristic

There were 72 subjects that would be analyzed. These subjects will be divided into two groups, treatment group and control group. Table 1. shows the characteristic of the subject before treatment.

Treatment Effect on the Five Dependent Variables

For multivariate analysis, Mancova test was used to determine whether the effect that occur on the five dependent variables was purely an effect from the give treatment which we can see on Table 2.

It was found that the supplementation of purple sweet potato extract had a pure effect in improving all the dependent variables, including decreased of the serum level of 8-OHdG by 1.611 pg/mL ($p < 0.001$); decreased the serum level of IL-6 by 3.320 pg/mL ($p < 0.001$); increased the total SOD serum level by 0.208 IU/mL ($p = 0.003$); improved the EEG image ($p = 0.004$); and decreased

Table 1. Subject characteristic

Subject Characteristic	Treatment group(n=37)	Control group(=35)	<i>p</i> *
Age (month), average (SD)	37 ±16.47	38±19.52	0.78
Gender (Male) n (%)	18 (48.6)	22 (62.9)	0.23
Epilepsycause, n (%)	22 (59.4)	23 (65.7)	0.21
Symptomatic epilepsy			
Neonatal seizure, yes n (%)	6 (16.2)	9 (25.7)	0.32
AED response, good, n (%)	13 (35.1)	13 (37.1)	0.86
Neuro stratus, normal, n (%)	20 (54.1)	18 (51.4)	0.82
Development delay n (%)	22 (59.5)	27 (77.1)	0.15
Below average	11 (29.7)	6 (17.1)	
Average	1 (2.7)	2 (5.7)	
Above average	3 (8.1)	0	
Very high			
Nutritional status, n (%)	14 (37.8)	10 (28.6)	0.54
Malnourished Good nutrition	23 (62.2)	25 (71.4)	
Head CT-Scan, normal n (%)	25 (67.6)	17 (48.6)	0.10
Geneticfactor, yes, n (%)	10 (27.0)	10 (28.6)	0.88
8-OhdG (pg/dL), average (SD)	6.93±0.28	6.90±0.31	0.86
IL-6 (pg/mL), average (SD)	8.16±0.39	8.15±0.44	0.80
SOD (IU/mL), average (SD)	1.57±0.11	1.60±0.08	0.25
Seizurefrequency, n (%)	12.14±8.12	10.26±6.02	0.27
EEG picture, normal, n (%)	25 (64.9)	24 (68.6)	0.22

SD = standard deviation; *)Chi square tests; **)Student's t-test

Table 2. Multivariate analysis of the treatment effect on the five dependent variable

Variable	Parameter Point Estimation	Estimasi Interval Estimation (95% CI)	p*
8-OHdG level (pg/mL)	-1.611	-1.867 ; -1.355	<0.001
IL-6 level (pg/mL)	-3.320	-3.691 ; -2.948	<0.001
SOD level (IU/mL)	0.208	0.075 ; 0.340	0.003
EEG image	-0.285	-0.478 ; -0.092	0.004
Seizure frequency at the 6th week (x/2 weeks)	-3.972	-6.039 ; -1.906	<0.001

CI = confidence interval; *Mancova analysis.

the seizure frequency at the end of the sixth week by 3.972 times ($p < 0.001$), compared to the control.

DISCUSSION

Seizure that occurs repeatedly in children with DRFE will cause an excessive free radical formation which can cause damage to neurons in the brain. One of the manifestation of neuronal damage due to oxidative stress is damage to cells DNA.¹² The damage in the DNA cause by an oxidation will lead to the 8-OHdG formation, so that the 8-OHdG can be used as biomarker of DNA damage in the cells.^{13,14} In this study, the mean serum level of 8-OHdG at baseline was 6.93 pg/mL in the treatment group and 6.90 pg/mL in the control group, there are no statistically significant difference. The normal level of serum 8-OHdG in healthy children is ranging from 0–70 pg/mL, so it can be said that the subjects in this study has already begun experiencing DNA damage in the brain's neurons due to oxidative stress despite the serum 8-OHdG level is still in the normal range.¹⁵ The results of this study indicate that subjects who were supplemented with the purple sweet potato water extract for six weeks compared to the control group, would have a greater reduction in serum 8-OHdG level with the difference margin of 1.589 pg/mL in the bivariate test and 1.611 pg/mL in the multivariate analysis, these two results statistically significant different. Several animal studies have already proved this issue, but there are still a very few clinical studies that have proved this issue. A clinical study only reported an association between

prolonged seizures and increased level of 8-OHdG in blood, cerebrospinal fluid and urine compared to normal people.¹⁶

The level of serum IL-6 is one of the biomarkers for chronic inflammation of the brain. In this study, the mean serum level of IL-6 at baseline was 8.16 pg/mL in the treatment group and 8.15 pg/mL in the control group, there was no statistically significant difference. These results are higher than the normal level of serum IL-6 which is 0.31- 5 pg/mL.^{17,18} The high level of serum IL-6 on this study subjects indicated that chronic inflammation did occur in DRFE patients. The results of this study indicate that subjects who were administered with the supplement for six weeks compared to the control group, will have a greater reduction in serum IL-6 level with the difference margin of 3.229 pg/mL in the bivariate test and 3.320 pg/mL in the multivariate analysis, both are different and statistically significant. Similar study using anthocyanin bilberry extract of 300 mg/day given to 118 healthy adults volunteer for 3 weeks, evidently decreased cytokine and chemokine levels regulated by nuclear factor-kB (NF-kB).¹⁹

Decreased of endogenous antioxidant including SOD is one of the result of oxidative stress in children with DRFE. The results of this study shows that the mean total of SOD serum level at the beginning of study was 1.57 IU/mL in treatment group and 1.60 IU/mL in control group that was not significantly different. These total SOD serum levels are markedly lower compared to total SOD serum for normal child which is 165-240 IU/mL.^{19,20} This study result demonstrates that

subject given with supplementation for 6 weeks compared to control showed greater increased in total SOD serum level with difference margin of 0.222 IU/mL in bivariate analysis and 0.208 IU/ml in multivariate analysis, both were statistically significant. There are only some studies on animals test including administration of purple sweet potato water extract increased antioxidant total in rabbit, increased SOD expression in rabbit markedly improved total antioxidant in rat.^{17,20} Existing clinical study found that enzymatic antioxidant levels in five progressive myoclonic epilepsy patients were lower than normal people.^{16,17} A case control study of 25 epilepsy patient aged 18-48 years old showed that total antioxidant status (TAS), GPx, GHS, SOD and CAT, significantly lower in epilepsy before treatment compared to healthy control.^{16,18,19}

Seizure in epilepsy may be distinguished into clinical seizure that can be apparently seen and electrographic seizure which is only present on EEG recording findings. Supplementation of purple sweet potato water extract that contain anthocyanin, not only has antioxidant and anti-inflammatory effects, but also has anticonvulsant property through its effect on GABA modulation.¹¹ Abnormalities in EEG images at the beginning of study were present in 35.1% of treatment group and 31.4% of control group, respectively, that did not differ statistically. Generally abnormalities in EEG findings of epileptic patient were found in 37% cases in first EEG examination, a proportion that was higher than the results in this study.^{2,4} This may be caused as not all subjects underwent EEG measurement as soon as clinical seizure was evident. Improvement in EEG findings after treatment was found 91.9% in treatment group and 60% in control group through bivariate analysis; this difference was statistically significant, and subsequently we also found significant difference on the basis of multivariate analysis. The only available study is study about administration of 600 mg/day vitamin E to 17 DRE patient regardless of his/her type for 1 month duration significantly decreased plasma MDA level, reduced seizure frequency and normalized EEG image in 11 patient.²¹⁻²⁴

Improvement of oxidative stress and chronic inflammatory conditions in the brain that underlie pathomechanism of convulsion recurrence,

as well as the improvement of EEG images then will rationally decreased the occurrence of clinical seizure.²⁵⁻²⁶

Mean frequency of seizure in initiation of study was 12.14 times/2 weeks in intervention group and 10.26 times/2 weeks in control group and no significant different statistically. After administered of purple sweet potato water extract at the end of second week, there was a decreased in seizure frequency of 1.499 times greater in treatment group compared to control, but this did not differ significantly. Additionally, other result showed decreased in seizure frequency 2.3 times higher in intervention group than in control at the end of fourth week and was statistically significant. Outcome at the end of sixth week particularly demonstrated that subject given with supplementation therapy compared to control experienced greater decreased in seizure frequency with difference margin of 4.5 times in bivariate analysis and 3.972 times in multivariate analysis, respectively. It is important to be noted that at the end of this study, we found 17 (46%) subjects with seizure free condition in intervention group and 5 (14.3%) subjects in control group. This in turn showed that supplementation with purple sweet potato water extract gave good impact in aiding DRFE patient aged 1-5 years to achieve remission compared to control. Until now, there are no any publications that report effect of purple sweet potato water extract on decreasing seizure frequency in DRFE children aged 1-5 years.²⁶⁻²⁷ The only available study is the used of oil extract of *Rosa Damascena*, *Nigella sativa* L, *Ginkobiloba* that were proven to decrease seizure frequency in DRE children, however additional dose of *Rosa Damascena* extract for refractory epileptic child could reduce seizure frequency, administration of *Citrus Auranturium* L extract for epileptic child increased latent period in tonic convulsion, treatment of *Chaiu-longu-muli-tang* extract in refractory epilepsy could reduce seizure frequency, treatment of herbal formulation capsule in 930 epilepsy children could decrease seizure frequency and duration.²⁸⁻³⁰

CONCLUSION

The use of supplementation of purple sweet potato extract will able to decrease the serum

level of 8-OHdG and the serum level of IL-6, increasing the total SOD serum level, improving the EEG image, decreasing the seizure frequency at the end of the sixth week, which then at the end will able to reduce the frequency of drugs resistant of focal epilepsy in children in future.

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