ETHANOL EXTRACT OF TIKEN LEAVES (*Fraxinus griffithii* Clarke) AS ANTICONVULSANT IN MICE

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ABSTRACT

Tiken plants (*Fraxinus griffithii* Clarke) has been used as traditional medicine in Indonesia or other countries. Research has demonstrated that tiken bark extract may prolong barbiturate sleeping time and also have anticonvulsant effects in mice. This research was carried out using ethanol extract of tiken leaves to study its anticonvulsant effect in mice. The study used five groups of experimental animals. The groups consisted of one control group, three treatment groups, and one standard group. The control group was given CMC Na suspension, treatment groups were given ethanol extract of tiken leaves at doses of 4000, 5000 and 6000 mg/kg body weight, respectively, the standard group was given Phenobarbital sodium solution at dose of 26 mg/kg body weight. Sixty minutes after treatment, all mice were induced using electroshock induced seizures. Anticonvulsant effect was determined by reduction in seizure duration. There were statistically significant differences in seizure duration between treatment, standard, and control groups. It can be concluded that the ethanol extract of tiken leaves have anticonvulsant effect in mice.

Key words : tiken, *Fraxinus griffithii* Clarke, anticonvulsant, electroshock.

INTRODUCTION

Seizures (convulsions) occur because of abnormal change of a group of cortical neurons that are not synchronized. Anything that disrupts the normal homeostasis and stability of the neuron will trigger hyperexcitability and seizures (Dipiro, 2008). Although the standard therapy can control seizures in 80% of the patients, millions of people in the United States are still suffering from uncontrolled epilepsy (Katzung, 2007).

Epilepsy is a common term for a group of disorders or diseases of central nervous system that arises spontaneously and recurrently with short episodes (called recurrent seizure) with the main symptom of declining until loss of consciousness. The attack/epileptic attack is usually accompanied by seizures (convulsions), autonomic hyperactivity, sensory or mental impairment, and always accompanied by a picture of abnormal and excessive EEG bursts (Syarif dkk., 2008).

Generally, there are two mechanisms (of action) of antiepileptic agents, which are potentiating inhibition (GABA-ergic mediated system) and decreasing excitation which then modifies the ion conduction of Na^+, Ca^{2+}, K^+ and Cl^- or neurotransmitter activity (Syarif dkk., 2008). Therapy of epilepsy

is a long-term treatment, in most cases, even a lifetime treatment. The medications used in epilepsy treatment is also not free from the side effects that should be avoided or prevented (Tjai & Rahardja, 2002).

Herbal medicines are generally safer than modern medicine, because the side effects induced by herbal medicines are less than modern medicines (Sari, 2006).

One of the medicinal plants that is suspected to contain the central nervous system active compound is *Fraxinus griffithii* Clarke, which is widely grown/available in various regions in Indonesia. It has various names in Java, such as *tiken* plant (*pohon tiken*), *bedali gombong*, and *orang-aring* plant (*pohon orang aring*) (Sutarjadi, 1980). In previous studies, the extract which is often used for testing the sedative and anticonvulsant effects is tiken bark extract. Although the locals initially made extracts from the bark and bark of branches of trees, however because it was difficult to obtain enough material, they then made extracts from twigs and leaves (Sutarjadi & Zaini, 1973). Therefore, a study needs to be done to determine whether the extract obtained from tiken leaves also has anticonvulsant effect which is the main symptom of epilepsy.

Pharmacodynamic identification of ligustroside, an iridoid glycoside, obtained from the isolation of tiken bark extract shows that this plant has antiseizure effect(Basori, 2003).

In this study, examination of the effectiveness of the ethanol extract of tiken leaves as an anticonvulsant was conducted on white male mice using the electroshock method. The electroshock device can cause electrical discharge in central nervous system, in which the discharge may result in the stimulation of serotonin, norephineprin, and acetylcholine, which further will stimulate the neurons and affects the motor activity and causing seizures (Thompson, 1990).

METHODS

Materials

The materials used in this study was 96% ethanol extract of tiken leaves (*Fraxinus griffithii* Clarke) obtained from kinetic maceration. The other materials that were also used are CMC-Na and Phenobarbital-Na.

Instruments

The instrument used in the study was electroshock device. The device is an inducer of the onset of seizure in mice. The electroshock device uses blunt electrodes which were attached to the eyes of mice for 0.2 seconds. The electrodes can discharge an electric current of 50 mA with a voltage of 100 volts which is set digitally.

Animals

The animals used in this study were sixty (60) white male mencit BALB/c mice, with 2-3 months old and weighing 20-30 g. The animals were obtained from a veterinarian center (PUSVETMA/Pusat Veterinaria Farma) in Surabaya .

The animals were healthy, which was characterized by clear eyes, no mucus seen from nose and mouth, no defects, the fur looks clean and smooth, not salivate continuously, and the animal looked active and always moving. The study was conducted on the animals which were naive or had never been used in any experiments or treatments.

Procedures

a. Preparation of Phenobarbital-Na solution

The dose of Phenobarbital-Na which were used for the mice was 26 mg/kg BW with a volume of 0.5 ml/20 g BW. Preparation of Phenobarbital-Na solution was carried out by dissolving Phenobarbital-Na in water.

b. Preparation of the suspension of ethanol extracts of tiken leaves

The dose of tiken extracts used in this study was based on previous study, using tiken bark extract at a dose of 3000, 4000, 5000, 6000 and 7000 mg/kg BW of mice (Basori, 2003).

In this study, the dosages used in the experiment (as treatment doses) was selected through orientation, in which three dosages was selected based on the shortest duration of seizures of mice. Based on the result of the orientation, the doses used were 4000, 5000 and 6000 mg/kg BW. The ethanol extract of tiken leaf was prepared by making a suspension of ethanol extract of tiken leaf and/with 1% CMC-Na.

c. Evaluation of anti-seizure effect of ethanol extract of tiken leaves in animals

The mice were randomly divided into 5 groups with each consisting of 10 mice, as follows: control group which was given a suspension of 1% CMC-Na; treatment group I which was given a suspension of 4000 mg/kg of tiken leaf extract; treatment group II which was given a suspension of 5000 mg/kg of tiken leaf extract, treatment group III which was given a suspension of 6000 mg/kg of tiken leaf extract, and the standard group were given a solution of sodium phenobarbital (Phenobarbital-Na). Sixty minutes after treatment, seizure was induced to all mice using electroshock device with electric current of 50 mA for 0.2 seconds, then the duration of seizures arising in mice was recorded.

d. Data Analysis

Data analysis method that was used is One Way Anova with $\alpha = 0.05$, then followed by LSD (Least Significant Difference) calculation.

RESULTS

Table 1. The duration of seizure of mice on control group

No. of mice	Duration of seizure (seconds)			
	Tonic	Clonic	Tonic-Clonic	Total
1.	16.16	-	14.96	31.12
2.	22.16	-	10.14	32.30
3.	18.68	-	11.87	30.55
4.	17.11	2.12	11.89	31.12
5.	14.32	3.81	14.65	32.78
6.	19.21	-	12.21	31.42
7.	21.77	-	9.09	30.86
8.	23.23	-	8.83	32.06
9.	23.19	-	9.64	32.83
10.	15.48	2.61	13.28	31.37
Mean ± SD				31.641±0.802

The duration of seizure of mice (seconds) of control group, treatment group, and standard group are presented in table 1, 2 and 3.

Table 2. The duration of seizure of mice on treatment group in various dose.

Dose	Duration of seizure (seconds)				
	Number of mice	Tonic	Clonic	Tonic-Clonic	Total
TREATMENT I 4000mg/kg BW	1.	20.69	-	3.00	23.69
	2.	19.23	-	5.00	24.23
	3.	18.31	2.88	3.12	24.31
	4.	19.25	-	5.85	25.10
	5.	22.22	2.00	-	24.22
	6.	13.44	3.05	7.22	23.71
	7.	16.92	-	6.35	23.27
	8.	20.09	-	3.91	24.00
	9.	20.17	2.03	2.11	24.31
	10.	19.37	-	4.98	24.35
	Mean ± SD				24.119±0.494
TREATMENT II 5000mg/kg BW	1.	18.02	4.00	-	22.02
	2.	18.22	2.78	-	21.00
	3.	22.03	-	-	22.03
	4.	19.83	2,17	-	22.00
	5.	18.89	2,00	-	20.89
	6.	19.33	2,57	-	21.90
	7.	16.82	2,13	3.63	22.58
	8.	10.21	-	12.25	22.46
	9.	18.38	2,14	1.86	22.38
	10.	15.00	2,00	7.19	24.19
	Mean ± SD				22.145±0.914
TREATMENT III 6000mg/kg BW.	1.	20.35	-	4.65	25.00
	2.	25.00	-	-	25.00
	3.	16.78	-	8.04	24.82
	4.	19.20	-	6.50	25.70
	5.	21.78	2.12	2.22	26.12
	6.	18.72	-	7.83	26.55
	7.	19.49	-	6.17	25.66
	8.	16.70	3.02	6.28	26.00
	9.	24.06	2.01	-	26.07
	10.	19.53	2.13	4.54	26.20
	Mean ± SD				25.712±0.589

Table 3. The duration of seizure of mice on standard group (Phenobarbital-Na).

Number of mice	Duration of seizure (seconds)			
	Tonic	Clonic	Tonic-Clonic	Total
1.	8.58	-	10.74	19.32
2.	7.72	3.09	8.46	19.27
3.	12.00	4.00	3.80	19.80
4.	10.35	10.43	-	20.78
5.	12.21	1.10	7.70	21.01
6.	11.58	2.01	6.32	19.91
7.	10.86	2.14	7.04	20.04
8.	12.36	2.02	5.23	19.61
9.	9.41	3.04	8.09	20.54
10.	7.83		11.70	19.53
Mean ± SD				19.981±0.609

Those results were further analyzed statistically using one way anova ($\alpha = 0.005$) and followed by calculation of LSD. The summary of the statistic result is presented in table 4 and the diagram of the mean duration of seizure of mice is presented in figure 1.

Tabel 4. Statistic Result of The duration of seizure of mice on control group, treatment group, and standard group.

(I) Group	(J) Group	Significance
Control	TLE* 4000	0,000
	TLE* 5000	0,000
	TLE* 6000	0,000
	Phenobarbital-Na	0,000
TLE* 4000mg/kg BW	TLE* 5000	0,000
	TLE* 6000	0,000
	Phenobarbital-Na	0,000
TLE* 5000mg/kg BW	TLE* 6000	0,000
	Phenobarbital-Na	0,000
TLE* 6000mg/kg BW	Phenobarbital-Na	0,000

*TLE = Tiken Leaf Extract

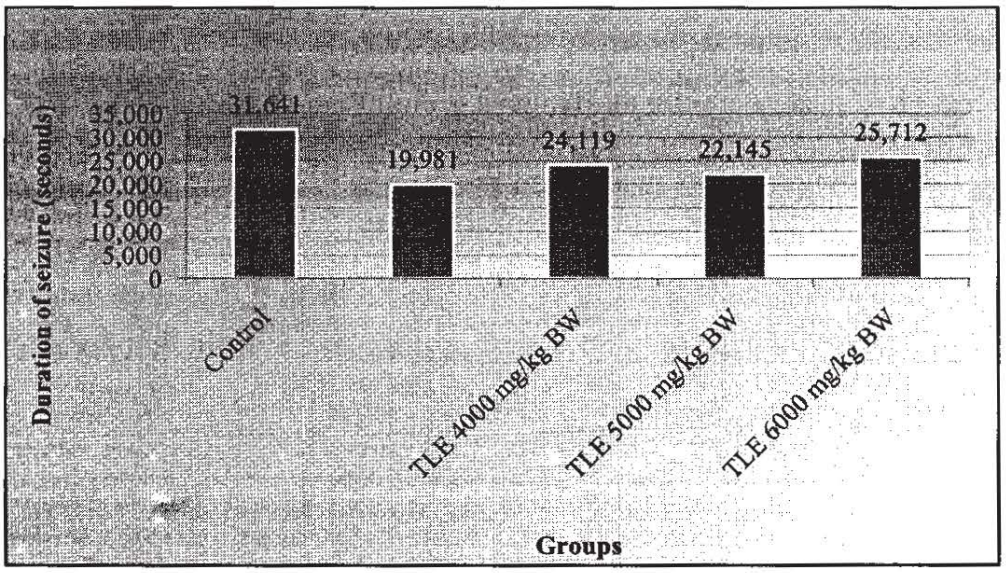

Figure 1. The diagram of the mean duration of seizure of mice of control, standard, and treatment group.

DISCUSSION

In this study, the examination of anticonvulsant effect of 96% ethanol extract of tiken leaves (*Fraxinus griffithii* Clarke) obtained from kinetic maceration was performed on mice in order to examine the effectiveness of tiken leaf extracts as an anticonvulsant. The evaluation was carried out with electroshock method using *Electroshock Seizure* device to induce seizures in mice.

Based on the previous research, it is known that the anticonvulsant effect of tiken bark extract (*Fraxinus griffithii* Clarke) is caused by the presence of ligustroside, an iridoid glycoside, so it can be expected that the anticonvulsant effect of tiken leaf extract is also caused by ligustroside.

Electroshock Seizure device as a seizure inducer in animals was used to cause seizure effects directly. The induction given was an electrical current of 50 mA for 0.2 seconds. The current was chosen because it can generate a maximal seizures in mice with minimal lethal possibilities. Blunt electrodes on Electroshock Seizure device were placed on the corneas of mice because the eye is associated with the second and third cranial nerve which connects the eye to the brain, so that it can stimulate an abnormal electrical burst on cerebral quickly. The electrical impulses are delivered to the motor organs, causing

abnormal motor activity and results in seizure. Seizures generated after the electrical induction are tonic, clonic, and tonic-clonic seizures. Tonic seizure is characterized by a rigid body state with the withdrawal of the front and rear limbs of mice, clonic seizure is characterized by a circular motion the front and rear legs with body position leaned to the rear or side, whereas the tonic-clonic seizure is characterized by the front and rear legs which are stomping repeatedly with the state body leaned sideways (Thompson, 1990).

The results of the duration of seizure of mice showed/demonstrated that the control group had the longest duration seizures which was for 31.641 seconds; the standard group had the shortest duration seizures which was for 19.981 seconds; the treatment group I had the duration of seizures of 24.119 seconds, treatment group II (22.145 seconds) and treatment group II (25.712 seconds). The means of duration of seizures were analyzed statisticaly and it is found that there were significant differences between all treatment groups; in which the control groups differed significantly with the treatment group and the standard group; as well as the comparison group differed significantly with the treament group. The treatment group I differed significantly with the treatment group II and III, as well as the treatment group II differed significantly with the treatment group III. It can be said that the ethanol extract of tiken leaves can provide/provides anticonvulsant effect in mice, although it is not as strong as the standard group which were given Phenobarbital-Na.

The mean duration of seizures of mice in the treatment group II was the lowest compared to treatment group I and III, this may imply that ethanol extracts of tiken leaves at a dose of 5000 mg/kg is the dose that gives the best therapeutic effect, while at doses of 6000 mg/kg BW ethanol extract of tiken leaves provide the mean duration of seizure were longer than in treatment group II, and this may raise some suspicions that (1) the receptor of drugs in the body was saturated or (2) biological and metabolism variation of each animal used in this study. Therefore, it is necessary to study further linearity of the relationship between the dose of ethanol extract of tiken leaves with the given therapeutic effects.

CONCLUSION

Based on the study that has been done, it can be concluded that the ethanol extract of tiken leaves (*Fraxinus griffithii* Clarke) can provide anticonvulsant effects in mice.

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