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ORIGINAL ARTICLE

The Difference of Effectivity between Nutmeg Seed Extract (*Myristica fragrans houtt)* and Diazepam based on Sleep Induction Time on Swiss webster Mice

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Abstract: According to the National Sleep Foundation in America, more than one third (36%) of young adults aged 18-29 years reported having difficulty getting up early (compared to 20% at 30-64 years old and 9% over 65 years). The National Sleep Foundation also states that in Indonesia the prevalence of insomnia sufferers reaches 70% at least once a week and 30 million people have difficulty sleeping every night. This study is an experimental study with a post-test only control group design. The samples used were 27 male Swiss webster mice which were divided into three groups. The treatment group was given nutmeg seed extract at a dose of 7.5 mg / kgBW; the positive control group was given diazepam, and the negative control group was given aquabidest. The results showed the difference in the average value of sleep induction time in the treatment group was 2.97 minutes, positive control group 5.06 minutes, and negative control group 8.43 minutes with p = 0.00. Conclusion: There is a significant difference between the effectiveness of nutmeg seed extract 7.5 mg / kgBW with diazepam based on the time of sleep induction in Swiss webster male mice.

Keywords: nutmeg seed extract, myristica fragrans houtt, sleep induction time.

INTRODUCTION

Sleep or rest is a basic need for all people so that the body can function normally after its daily activities because, during sleep, the body performs the process of recovery and restoration of energy to be in optimal condition. Good sleep patterns can help maintain health.[1] Sleep patterns are models, forms or ways of sleep that persist for a relatively long period, including sleeping and waking schedules, sleep rhythm, frequency in a day, maintaining sleep conditions, and sleep satisfaction.[2] Quality sleep patterns can be seen from how deep a person is sleeping where there are no signs of problems in sleep, while in terms of quantity can be assessed in terms of the number of hours of sleep.[3]

Some factors that can affect the quality and quantity of one's sleep are psychological stress (diseases and situations that cause stress), age, diet, physical activity, consuming caffeine, alcohol, environment, lifestyle, smoking, illness, and drug use.[4,5] The prevalence of stress and depression or anxiety disorders has a high enough rate.

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According to WHO data in 2015, there were around 4.4% of the world's population or 322 million people affected by depression and around 3.6% of the world's population or 264 million people affected by anxiety.[3]

So far, the therapy given to people with insomnia is hypnotic drugs and cognitive behavioral therapy (CBT). The use of hypnotic drugs has proven to be more effective compared to other therapies.[6] However, the use of existing hypnotic drugs is a problem that needs to be considered such as using hypnotic drugs without knowing the underlying cause of the disease or the emergence of drug abuse which is now increasingly prevalent in the community. Seeing from the aforementioned events, traditional medicine is needed as an alternative treatment that is effective, safe, inexpensive and easily available to reduce these problems.[7,8,9]

Nutmeg (*Myristica fragrans houtt*) is often used by the community as a medicine to calm or overcome insomnia.[10,11] Nutmeg seeds contain substances such as myristicin, elemicin, and safrole.[12] Research conducted by Rahadian in 2013 showed that nutmeg seed extract at a dose of 7.5mg / 25gBB can shorten the sleep induction time in male mice of the Wistar strain (*Swiss webster*).[13] But it has not been proven whether the sedative-hypnotic effect of nutmeg seed extract at a dose of 7.5 mg/25 kg BW is more effective compared to hypnotic drugs such as benzodiazepines, cyclopirrolone, an imidazopyridine, therefore researchers are interested in examining the comparison of the effectiveness of sedative-hypnotic nutmeg extract (*Myristica fragrants houtt*) with diazepam on Swiss webster male mice.[14,15]

METHODS

This research is a true experimental research design with a post-test only control group design. The research was carried out in the Laboratory Animal Management Unit of the Department of Pharmacology, University of Muhammadiyah North Sumatra and the Biochemistry Laboratory, Faculty of Medicine, University of Muhammadiyah, North Sumatra in April - December 2018.

Nutmeg plants were identified in the plant laboratory of the Faculty of Mathematics and Natural Sciences, University of North Sumatra. The making of nutmeg seed extract was carried out at the Biochemical Laboratory of the Faculty of Medicine, University of Muhammadiyah North Sumatra. The nutmeg seed extract is made by the nucleation method and the distillation method. The making of diazepam solution was carried out at the Laboratory Animal Management Unit, Department of Pharmacology, University of Muhammadiyah North Sumatra.

The research sample used in this study was male Wistar strain mice (Swiss Webster) who met the inclusion criteria in the form of the male sex, age 2-3 months, body weight 25-35 grams, healthy physical condition and did not appear anatomically deformed and had never been used as a subject of prior research. Mice that died during the study will be excluded. Mice were divided into 3 groups, namely the treatment group that was given palladic seed extract with a dose of 7.5 mg / kgBW as much as 0.5 ml, the positive control group that was given Diazepam at a dose of 0.013 mg/kgBW as much as 0.5 ml and the negative control group was given aquabidest liquid as much as 0.5 ml. Each is given orally through a probe.

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Sleep induction time is calculated using a stopwatch starting from the time the liquid is given until the mouse has no response to light and there is no response when the body of the mouse is reversed.

RESULTS

This study used a sample of 27 Swiss webster mice and divided each consisted of 9 mice per group with an average body weight value of 30.9 grams of mice. The negative control group is the group given the aqua dest. The positive control group is the group given diazepam. The treatment group is the group that was given nutmeg seed extract. The average body weight of mice per group can be seen in Table 1.

Table 1. Mean Weight of Mice

Group	n	Average Weight (in grams)
Negative Control	9	30,9
Positive Control	9	31
Treatment	9	30,9

Based on sleep induction time measurement results, the average value of the negative control group was 8.43 minutes, the positive control group was 5.06 minutes and the treatment group obtained 2.97 minutes. In the One-way Anova analysis test, the value of p = 0,000 (p <0.05) means that there are significant differences in sleep induction time in the three data groups.

Table 2. The difference in Sleep Induction Time Average

Groups	n	Sleep Induction Time ± sd (in minutes)	p
Negative Control	9	8,43 ± 0,5969	
Positive Control	9	5,06 ± 0,3597	0,00
Treatment	9	2,97 ± 0,2427	

In the Post Hoc analysis test, it was seen that the treatment group had a difference of 2.09 minutes faster sleep induction time when compared with positive controls. The negative control group had a difference of 5.46 minutes with the treatment group, and a difference of 3.36 minutes with positive control. This is also supported by the value of p = 0,000 (p <0.05) which can be interpreted that each group has a significant difference.

Table 2. Post Hoc Analysis Test Results for Sleep Induction Time

Group	Average Difference	CI 95%		p
		Minimum	Maximum	
Positive Control vs. Negative Control	-3,36	-3,77	-2,94	0,00
Treatment vs. Negative Control	-5,46	-5,87	-5,04	0,00
Treatment vs. Positive Control	-2,09	-2,51	-1,68	0,00

DISCUSSIONS

Based on the results of the calculation of sleep induction time on Swiss webster mice, that the data group has a value of p=0,000 (p <0.05) which means that there are significant differences in sleep induction time in the data group. This is not in line with research by Sayidin 2009 which reported that sleep induction time in the data group has a value of p=0.947 (p> 0.05) which means there is no significant difference in sleep induction time in the data group.[14]

In the results of the study, it was concluded that the treatment group that was given nutmeg seed extract at a dose of 7.5 mg/kgBW gave the shortest sleep induction

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time compared to the control group. This is per research by Rahadian 2009 which reported that nutmeg seed extract at a dose of 7.5 mg/25grBW can shorten the sleep induction time in mice.[15] This is in line with research by Weiss 2002 which reported that the content of substances contained in nutmeg, namely myristicin, elemicin, and safrole as much as 2-18% proved to be stimulating sleep with a dose of less than 5 gr.[18] This is reinforced by the explanation shown by Winarti and Nurdjanah in 2005 which states that in nutmeg essential oils about 5-15% contain compounds including pinene, sabinene, camphene, myristicin, elemicin, iso-elemicin, eugenol, isoeugenol, methoxy-eugenol, safrole, dimeric poly-propanoate, lignans, and neolignans. Some compounds have various effects that can be used as a sedative-hypnotic drug.[11]

The results of this study are not in line with research by Sayidin 2009 which reported that nutmeg seed extracts with a dose of 1 mg/kgBW, 2 mg/kgBW, and 3 mg/kgBW did not have a significant effect on the sleep induction time in mice.[14] This is also not in line with research by Adnyana 2012 which reported that nutmeg seed extract at a dose of 7.80 µL/kgBW and 16.90 µL/kgBW did not provide a significant shortening of sleep induction time compared to the control group..[13]

This study has limitations such as the dose of nutmeg seed extract used in this study is only one variation, so no known lethal dose or side effects from the administration of nutmeg seed extract in mice. Another limitation is that the tools used in this study are limited. The tool that can be used to clarify the sedative effect of nutmeg seed extract is an electroencephalogram (EEG) which can see the activity of brain waves in mice after being given nutmeg seed extract.

CONCLUSIONS

Based on the results of the research and discussion that has been explained, it can be concluded that there is a significant difference between the effectiveness of nutmeg seed extract 7.5 mg/kgBW with diazepam based on the time of sleep induction in Swiss webster male mice.

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