EFFECT OF RED GINGER (Zingiber officinale Rosc. Var Rubrum) ETHANOL EXTRACT ORSILDENAFIL IN LIBIDO: A COMPARATIVE STUDY USING MALE WHITE RATS (Rattus norvegicus) MODEL WITH DIABETES MELLITUS

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ABSTRACT

Objective: *To compare the effect of red ginger ethanol extract and Sildenafil on increasing the libido of diabetic rat models and determine the dose that significantly affects the increase in libido of diabetic rat models.* ***Materials & Methods:*** *This study is an experimental was conducted on 30 male Sprague dawley white rats divided into 6 groups, namely normal control group, negative control group, sildenafil positive control group, 200 mg ginger group, 400 mg ginger group and 600 mg ginger group study consisting of test animal groups: normal control group; negative control; positive control with sildenafil administration, and treatment groups consisting of: dose I (200mg/kgBB); dose II (400mg/kgBB) and, dose III (600mg/kgBB). All groups except the normal control received alloxan induction at the initial stage of testing. The effect of increasing the libido of rats is seen from sexual activity including: latency of copulation, latency of riding (climbing) and frequency of riding.* ***Results:*** *The results of this study indicate that the administration of red ginger ethanol extract at a dose of 400mg/kgBB or 600mg/kgBB has the same potential as sildenafil in increasing the libido of diabetic rat models.* ***Conclusion:*** *The administration of red ginger ethanol extract at a dose of 400mg/kgBB or 600mg/kgBB has the same potential as sildenafil in increasing the libido of diabetic rat models.*

Keywords: *Red ginger, libido, diabetic rat models.*

ABSTRAK

Tujuan: *Mengetahui perbandingan pengaruh ektrak etanol jahe merah dan Sildenafil terhadap peningkatan libido model tikus diabetes dan mengetahui dosis yang signikan mempengaruhi peningkatan libido model tikus diabetes.* ***Bahan & Cara:*** *Studi ini merupakan eskperimental yang terdiri atas kelompok hewan uji: kelompok kontrol normal; kontrol negatif; kontrol positif dengan pemberian sildenafil, dan kelompok perlakuan yang terdiri dari dosis I (200mg/kgBB); dosis II (400mg/kgBB) dan, dosis III (600mg/kgBB). Semua kelompok kecuali kontrol normal mendapat induksi aloksan pada tahap awal pengujian. Efek peningkatan libido tikus dilihat dari aktivitas seksual meliputi latensi percumbuan (introduction), latensi penunggangan (climbing) dan frekuensi penunggangan.* ***Hasil:*** *Penelitian ini dilakukan pada 30 ekor tikus putih jantan galur Sprague dawley yang dibagi menjadi 6 kelompok, yaitu kelompok kontrol normal, kelompok kontrol negatif, kelompok kontrol positif sildenafil, kelompok jahe 200 mg, kelompok jahe 400 mg dan kelompok jahe 600 mg.Hasil penelitian ini menunjukkan bahwa pemberian ekstrak etanol jahe merah dosis 400mg/kgBB atau 600mg/kgBB memiliki potensi yang sama baik dengan sildenafil dalam meningkatkan libido model tikus diabetes.* ***Simpulan:*** *Pemberian ekstrak etanol jahe merah dosis 400mg/kgBB atau 600mg/kgBB memiliki potensi yang sama baik dengan sildenafil dalam meningkatkan libido model tikus diabetes.*

Kata Kunci:*Jahe merah, libido, model tikus diabetes.*

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INTRODUCTION

Diabetes mellitus (DM) is the most common risk factor for sexual dysfunction in men. The increased risk of erectile dysfunction is threefold in diabetic men, compared to non-diabetic men.[1] The prevalence of erectile dysfunction (ED) is highly prevalent in at least 50% of men with DM.[2] The disorder is defined as the inability to achieve and maintain an erection sufficient for sexual performance. ED can affect physical and psychosocial health and may have a significant

impact on the quality of life of sufferers and their partners.[3]

Decreased libido and orgasmic dysfunction are commonly associated with erectile dysfunction in patients with type 2 diabetes.[4] Some triggers of decreased libido are relationship problems, stress, anxiety disorders, depression, menopause, sexual problems, birth problems, breastfeeding, certain diseases (diabetes mellitus, hypertension, cancer, thyroid disorders), medications and contraceptives, alcohol and drugs.[5] Lifestyle changes, diabetes control, and treatment of hypogonadism are important first steps in ED management.[6] Phosphodiesterase type 5 inhibitors (PDE5i) such as sildenafil are the first-line treatment of choice in ED and intracavernous administration of vasoactive drugs is used as second-line treatment when PDE5i administration does not respond well.[6-7]

Red ginger Zingiber officinale Roscoe (Zingiberaceae) has an aphrodisiac effect and is used in overcoming sexual dysfunction problems.[8-10] Ginger can provide a circulatory stimulant effect so that it can increase libido.[11] Sutyarso et al. reported that the administration of ginger extract to male mice showed very high sperm quality, viability, motility and morphology compared to the control group ($P < 0.001$).[12] Reviewing the potential of red ginger as an aphrodisiac, the researcher considers it necessary to develop studies related to the effects of red ginger as an aphrodisiac.

OBJECTIVE

This study aims to compare the effect of red ginger ethanol extract and Sildenafil on increasing the libido of diabetic rat models and determine the dose that significantly affects the increase in libido of diabetic rat models.

MATERIAL & METHODS

The test animals used were wistar rats. Before being given the treatment, the rats were acclimatized for seven days to avoid stress on the rats that could affect the results of the study. Rats were placed in laboratory cages in the Faculty of Mathematics and Natural Sciences and given standard food and drink. A total of 30 test animals were divided into 6 groups including normal control, negative control, sildenafil group, P1, P2 and P3. Normal control group was an animal test that only given standard food and drink. Negative control group was an animal test that given alloxan-induced. Sildenafil group was an animal test that induced with alloxan and given sildenafil 5mg/KgBW. The sildenafil group received sildenafil one hour before observation.While P1-P3 or treatment group that induced by alloxan and given ginger extract with 3 variations in dose, which is P1 given 200mg/KgBB of ginger ethanol extract; P2 given 400mg/kgBB of ginger ethanol extract; and P3 given 600mg/Kg of ginger ethanol extract.The treatment group received red ginger ethanol extract for 21 days.

Testing the pharmacological effects of red ginger extract was initiated by making a rat model of diabetes mellitus. Rat test animals were induced with alloxan by a single intraperitoneal (i.p) injection of freshly prepared alloxan solution in normal saline at a dose of 120 mg/kgBB.[13] Since alloxan is capable of producing fatal hypoglycemia due to massive pancreatic insulin release, rats were treated orally with 20% glucose solution (5-10 ml) after 6 hours. Rats were then maintained for the next 24 hours with 5% aqueous glucose solution to prevent hypoglycemia.

Blood glucose levels of rats were measured enzymatically using an Auto Check glucometer with a 10µL sample of blood taken from the tail vein of rats. Blood glucose levels will be measured on the last day of acclimatization and after three days post alloxan induction. Blood glucose levels of normal rats with a range of 115 ± 169 mg/dL.The state of diabetes mellitus in experimental animals induced by alloxan can appear in a fast time, namely within 72 hours (3 days) The experimental animals will be said to be diabetic if blood glucose levels > 200 mg/dL.[14]

In this study, the Posttest Only Control Group Design was used. Data collection was only carried out at the end of the study involving the subject group that was given experimental treatment (experimental group). This study is a comparative study that aims to see differences in the output level of sexual activity of male rats. This study is an analytical study with Research Ethics Approval which will be submitted to the Research Ethics Commission of the Faculty of Medicine, University of Lampung.

Samples of red ginger rhizomes (Zingiber officinale rosc. var rubrum) were obtained from the Center for Research and Development of Medicinal Plants and Traditional Medicines Tawangmangu, Surakarta, which had been determined. Fresh red ginger rhizomes were wet sorted using running water, until there were no impurities attached. Then the rhizomes were chopped and dried in the sun to remove the water content in the rhizomes, because it would interfere during maceration. The dried rhizomes were blended until a fine powder of ginger

rhizomes was obtained. To find out that the powder is completely qualified, the drying weight loss is measured on the powder.

A total of 5 kg of red ginger rhizome samples were macerated using ethanol solvent for 3 days, after maceration filtered with whatman paper no 45, the results of the filter obtained liquid extract, which was then forgotten by the solvent with a rotary evaporator until a thick extract was obtained. The results of the filter obtained residue, the rest of this residue in soxhletation using chloroform until the solvent color changes to perfect. Then the obtained liquid extract is evaporated using a rotary evaporator until it becomes a thick extract. Extract results from each solvent were tested for ash content, water content, and drying shrinkage.

This study was conducted for 21 days (3 weeks) because based on research for 14 days (2 weeks) there has been a decrease in the average level of testosterone hormone in diabetic rat models and the administration of red ginger ethanol extract can already have a significant effect on increasing libido in rats for 7 days.[15-16]

Observation of the level of libido of rats was carried out on the last day of the study (day 22) at 19.00 WIB. At the time of observation will produce data in the form of latency of copulation (introduction), latency of riding (climbing) and frequency of riding.

The latency of copulation, which begins when male and female rats are put together in a box and given a middle partition, then the partition is opened and the occurrence of copulation is marked by licking the outside of the female genitals, until the smell of the mouth to the neck. This test is carried out for 15 minutes.

Riding latency, which starts when male and female rats are put together in a box with a partition that has been opened until the riding occurs or the male rat rides the female rat's body from behind. This test was conducted for 15 minutes.

Frequency of riding, which is measured by looking at the number of rides performed during the 15-minute test.

Data on dependent and independent variables were tested for normality and homogeneity with the Shapiro-Wilk test because the number of samples <50. If the data is normally distributed and the average is homogeneous, then proceed with the One-way Anova test. If the results mean $p < 0.05$, then proceed with the LSD Post Hoc test. If the data is not normally distributed or not homogeneous, it will continue with the Krruskal Wallis test. If the result is significant $p<0.05$, it will be continued with the Mann Whitney test.

RESULTS

Table 1. Observation results of rat libido after giving red ginger ethanol extract.

Rat Group	Copulation Latency (seconds)	Parameter Riding Latency (seconds)	Riding Frequency (number)
Normal control			
1	22	60	18
2	32	130	14
3	56	112	15
4	50	114	20
5	65	190	11
Negative control			
1	600	695	4
2	620	780	3
3	690	700	1
4	650	820	2
5	730	850	1
Sildenafil group			
1	61	200	17
2	75	365	14
3	38	125	14
4	45	220	8
5	75	300	6
P1 (Ginger 200 mg)			
1	160	300	10
2	200	350	11
3	282	200	16
4	300	261	11
5	301	209	15
P2 (Ginger 400 mg)			
1	95	400	13
2	36	137	11
3	50	157	16
4	52	125	14
5	45	200	15
P3 (Ginger 600 mg)			
1	96	350	12
2	40	137	10
3	50	157	16
4	51	130	14
5	47	221	16

This study was conducted on 30 male Sprague dawley white rats divided into 6 groups, namely normal control group, negative control group, sildenafil group, 200 mg ginger group, 400 mg ginger group and 600 mg ginger group. Observations were made at 19:00 - 21:00 WIB at the Animal House, Faculty of Mathematics and Natural Sciences, University of Lampung using a video recorder. Graphic 1-6 shows the results of observations of rat libido after administration of ethanol extract of red ginger.

After observing the level of libido of male white rats, there were differences in the level of libido between the normal control group, negative control, sildenafil, and treatments 1, 2, and 3 given red ginger ethanol extract. Table 1 shows the average libido parameters of rats after the administration of red ginger ethanol extract.

The results of the libido level parameters of each group of rats will be analyzed statistically. The first test performed is the normality test using the Shapiro Wilk Test, obtained the following data shown in Table 2.

Table 2. Mean libido parameters of rats after administration of ethanol extract of red ginger.

Rat Group	Parameter (Mean ± SD)		
	Copulation Latency (seconds)	Riding Latency (seconds)	Frequency of Ridden (number)
Normal control	45.00 ± 17.63	121.20 ± 46.61	15.60 ± 3.50
Negative control	658.00 ± 52.63	769.00 ± 69.85	2.20 ± 1.30
Sildenafil	58.80 ± 16.97	242.00 ± 92.77	11.80 ± 4.60
P1	248.60 ± 64.64	264.00 ± 62.89	12.60 ± 2.70
P2	55.60 ± 22.87	203.80 ± 113.32	13.80 ± 1.92
P3	56.80 ± 22.33	199.00 ± 91.72	13.60 ± 2.60

Table 3. Results of post hoc lsd test of libido parameter data of riding latency rats after administration of ethanol extract of red ginger.

Group	Normal control	Negative control	Sildenafil	P1	P2	P3
Normal control	-	0.000	0.030	0.012	0.127	0.149
Negative control	0.000	-	0.000	0.000	0.000	0.000
Sildenafil	0.030	0.000	-	0.667	0.471	0.418
P1	0.012	0.000	0.667	-	0.260	0.225
P2	0.127	0.000	0.471	0.260	-	0.927
P3	0.149	0.000	0.418	0.225	0.927	-

Table 4. Results of Mann Whitney Post Hoc Test for libido parameter data of latency copulation of rats after administration of ethanol extract of red ginger.

Group	Normal control	Negative control	Sildenafil	P1	P2	P3
Normal control	-	0.000	0.798	0.009	0.955	0.928
Negative control	0.000	-	0.000	0.000	0.000	0.000
Sildenafil	0.798	0.000	-	0.013	1.000	1.000
P1	0.009	0.000	0.013	-	0.010	0.011
P2	0.955	0.000	1.000	0.010	-	1.000
P3	0.928	0.000	1.000	0.011	1.000	-

Table 5. Mann Whitney Post Hoc Test results libido parameter data frequency of riding after administration of ethanol extract of red ginger.

Group	Normal control	Negative control	Sildenafil	P1	P2	P3
Normal control	-	0.003	0.692	0.667	0.901	0.897
Negative control	0.003	-	0.047	0.002	0.000	0.001
Sildenafil	0.692	0.047	-	0.999	0.933	0.965
P1	0.667	0.002	0.999	-	0.957	0.988
P2	0.901	0.000	0.933	0.957	-	1.000
P3	0.897	0.001	0.965	0.988	1.000	-

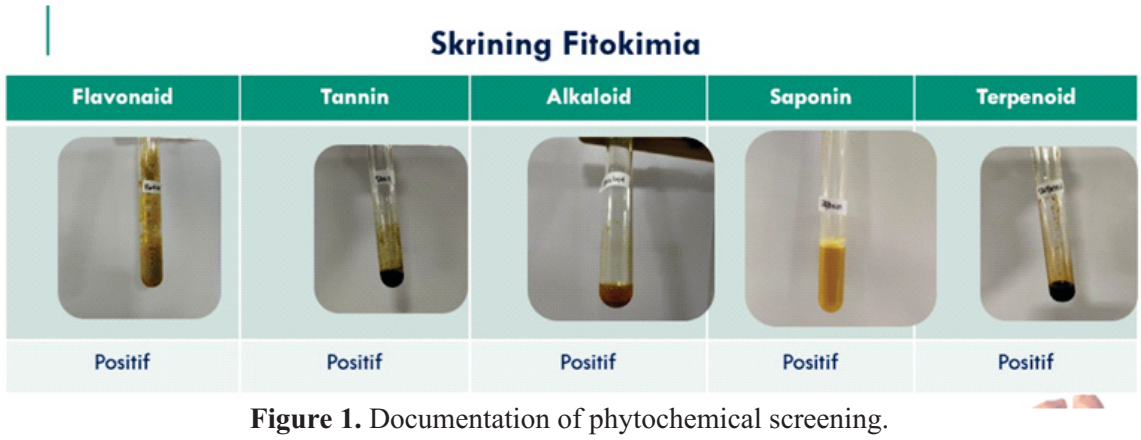

Figure 1. Documentation of phytochemical screening.

Figure 2. Documentation of red ginger extract sample preparation.

Figure 3. Documentation of induction of mice with alloxan and oral administration of red ginger extract.

Fugure 4. Documentation of pharmacological test parameters observation.

DISCUSSION

In the observation of copulation latency, riding latency and frequency of riding in 6 groups. It was found that the fastest time in the latency of copulation was in the normal control rat group in 22 seconds and the longest time in the latency of copulation in the negative control rat group was 730 seconds (12 minutes 16 seconds). For riding latency, the fastest time was obtained in the normal control rat group with 60 seconds (1 minute) and the longest time in the negative control group was 850 seconds (14 minutes 16 seconds). Meanwhile, for the frequency parameter, the highest number of riding was obtained in the normal control group with 20 riding and the least number was the negative control group with one riding.

The results obtained the average of each libido parameter of rats after the administration of ethanol extract of red ginger for 21 days. The negative control group was the group with the longest latency of copulation and riding among other groups, namely 658.00 seconds for copulation latency and 769.00 seconds for riding latency. And the negative control group has the least average frequency of riding among other groups with an average of 2.20 times in 15 minutes of observation.

In the group of diabetic rats that were not given red ginger ethanol extract where diabetic rats were not given red ginger ethanol extract showed a decrease in libido. Because in diabetics there will be a state of hyperglycemia that will stimulate an increase in the activity of Protein Kinase-C (PKC), TNF α which can cause disruption of the integrity of the structure and function of the vascular and peripheral nervous system. In addition, there can also be a decrease in Insulin-like Growth Factor (IGF-I) expression due to insufficient or insensitive insulin causing a decrease in Leydig cell response to LH. With insulin resistance in the testes there will also be a decrease in Stem Cell Factor (SCF) signaling so that it will affect the replication of Leydig cells in the testes causing a decrease in testosterone hormone production, besides that it also causes a reduction in androgen receptors on Leydig cells so that it will also affect testosterone hormone levels.[17]

Testosterone is needed for the awakening of libido, testosterone can increase sexual excitement (sexual eroticism) and sexual awareness. Decreasing the amount of testosterone causes reduced accumulation of testosterone in the hypothalamus and cerebral cortex, as a result the part that activates brain metabolism and regulates libido becomes less

active so that there is an obstacle or decrease in libido.[18]

After conducting Post-Hoc tests in the form of LSD and Mann-Whitney on all libido parameters and groups of rats, there was a significant acceleration in the parameters of latency of copulation and riding in the group of diabetic rats treated with red ginger ethanol extract and a significant increase in the frequency of riding compared to the group of diabetic rats that were not treated with red ginger ethanol extract.

In treatment group 1 (P1), namely rats given red ginger ethanol extract at a dose of 200 mg/KgBB for 21 days, the average latency of copulation for 248.60 seconds, latency of riding for 264.00 seconds and frequency of riding a total of 12.60 times in 15 minutes of observation. In treatment group 2 (P2), namely rats given red ginger ethanol extract at a dose of 400 mg / kgBB for 21 days, the average latency of copulation for 55.60 seconds, latency of riding for 203.80 seconds and frequency of riding a total of 13.80 times in 15 minutes of observation. In treatment group 3 (P3), namely rats given red ginger ethanol extract at a dose of 600 mg/KgBB for 21 days, the average latency of copulation for 56.80 seconds, latency of riding for 199.00 seconds and frequency of riding 13.60 times in 15 minutes of observation.

These results show that the time on the parameters of the latency of copulation and latency of riding in the diabetic rat group given red ginger ethanol extract is faster than the average latency of copulation and riding in the diabetic rat group that was not given red ginger ethanol extract and the frequency of riding in the diabetic rat group given red ginger ethanol extract is more than the average frequency of riding in the diabetic rat group that was not given red ginger ethanol extract. So that the results obtained from all parameters of rat libido in the group of diabetic rats given red ginger ethanol extract increased libido compared to the group of diabetic rats that were not given red ginger ethanol extract.

In this study, diabetic rats given red ginger ethanol extract experienced an increase in libido compared to the positive control group that was not given red ginger ethanol extract, this is because red ginger contains antioxidants.[19] Ingredients in ginger rhizomes that are considered to haveantioxidant and anti-inflammatory activities include zingerone, shogaol, and gingerol.[20]

Antioxidants function to reduce oxidative damage due to hyperglycemia. Hyperglycemia is involved in the formation of free radicals. Increased levels of antioxidants can prevent clinical complications in DM, including inhibiting microvascular complications, reducing the incidence of coronary heart disease, improving the autonomic nervous system in the heart, and vasodilating blood vessels.[2] This is in line with several previous studies that studied the hypoglycemic potential of red ginger in rats that have been induced into diabetes that with doses between 300 - 500 mg/kgBB can already have an effect on reducing blood glucose levels effectively in diabetic rats.[20-21]

In addition to the phenolic content of red ginger which is antioxidant in red ginger there are also aphrodisiac compounds that can increase testosterone hormone levels and encourage sexual behavior in men. The active compounds contained in red ginger that act as aphrodisiacs are flavonoids and alkaloids.[22] Flavonoids and alkaloids not only have central action but also have peripheral action, namely by helping relax the corpus cavernosum which triggers an erection. The central mechanism possessed by alkaloids is to increase the release of nitricoxide (NO) from endothelial and nerve endings through activating nitric oxide synthase. Especially alkaloid compounds dehydrochorildamine, berberine, jatrorizin, and talifendin can actively interact with the enzyme nitric oxide synthase.[23]

In the process of erection, NO is a neural mediator whose principle can cause relaxation of the smooth muscles of the penile cavernosum and penile blood vessels so as to cause a full erection. Through these various mechanisms, the active compounds in red ginger cause an increase in libido so that it can encourage sexual behavior and is called the aphrodisiac effect. The administration of red ginger extract with a concentration of 70% can increase sexual arousal in men who experience sexual dysfunction in general.[24]

Furthermore, the Post-Hoc test found significant differences in all parameters of libido between groups of diabetic rats given red ginger ethanol extract and groups of diabetic rats that were not given red ginger ethanol extract. So based on this study that at a dose of 400 mg/kgBB red ginger ethanol extract can have an increasing effect on the libido of diabetic white rats.

When compared with the positive control group given sildenafil, the treatment groups given red ginger ethanol extract at a dose of 400mg/kgBB and a dose of 600mg/kgBB did not have significant differences in results for the parameters of intercourse latency, riding latency and riding

frequency. The results indicate that the administration of red ginger ethanol extract at a dose of 400mg / kgBB or 600mg / kgBB has the same potential as sildenafil in increasing the libido of diabetic rat models.

CONCLUSION

In conclusion, the administration of red ginger ethanol extract at a dose of 400mg / kgBB or 600mg / kgBB has the same potential as sildenafil in increasing the libido of diabetic rat models.

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