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Research Article

Aphrodisiaca Activity of *Momordica charantia* L. and *Areca catechu* L. Ethanolic Extract Againts Blood Pressure and Body Weight of White Mile Rats

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ABSTRACT

Advances in the discovery of herbal medicine and the increasing popularity of traditional medicines have made access to traditional medicines in the market increasingly easier. Bitter melon and areca nut are known to have many benefits and potential as natural medicine. Previous studies has shown the aphrodisiac effects of these two natural ingredients. This research aimed to determine the additional effects, particularly on blood pressure and body weight of rats, when bitter melon and areca nut are administered as aphrodisiacs. Test animal retrieval techniques based on complete randomized design (RAL). Blood pressure was measured using the CODA® instrument on 25 white rats divided into 5 treatment groups, namely the control group (CMC Na 0.5 % 0.5 % w/v), the bitter melon extract group at a dose of 280 mg / kg BW, the areca nut extract group at a dose of 50 mg/kg 50 mg / kg BW, the mixed bitter melon and areca nut extracts group (1: 1), and the X-Gra® group. Blood pressure profiles measured included systolic and diastolic blood as well as changes in rat body weight before and after treatment. The results of the study of systole and diastole blood pressure parameters and rat body weight in groups I, II, III, IV, V analyzed using the Tukey HSD method obtained results that were not significantly different (sig> 0.05) in all groups. Based on this study, it was concluded that the aphrodisiac activity of bitter melon and areca nut seeds did not significantly influence changes in blood pressure, systole and diastole, and body weight rats.

Keywords: Areca nut seeds; Bitter melon; Blood pressure; Diastole; Systole

INTRODUCTION

Erectile dysfunction is one of the factors contributing to disharmony in marital relationships. There is epidemiological studies that support the high prevalence of erectile dysfunction. The global prevalence of erectile dysfunction is 3–7.6 % (Kessler, 2019). Meanwhile, the widely reported prevalence of erectile dysfunction in Asia ranges from 2 % to 88 % (Park et.al, 2011). The prevalence of erectile dysfunction in Indonesia is around 35.6 % (Birowo, 2019).

Decreased sexual arousal can be overcome by administering aphrodisiac drugs which can increase sexual arousal and longer erections. Aphrodisiacs are agents that can increase sexual arousal or erectile dysfunction (Kotta, 2013). Drugs used to treat erectile dysfunction can cause vasodilation cavernous vein vasodilation and are contraindicated for hypertensive patients who take antihypertensive drugs because they will cause a significant decrease in blood pressure. The act of performing sexual activity itself make a big contribution and greatly influences cardiovascular risk, which is of course related to blood pressure regulation (Ajeigbe et al.. 2021).

Blood pressure is said to be normal if a person has a systolic blood pressure of at least 120 mmHg and/or a diastolic blood pressure of at least 80 mmHg. If blood pressure is not in the normal range, it will be

very dangerous for the body (Indonesia P.D.H, 2019). Erectile dysfunction treatment can be done in two ways, namely pharmacological and non-pharmacological. Pharmacological treatment is the management of hypertension using chemical drugs. This non-pharmacological treatment uses traditional plants or fruits (Leisegang and Finelli , 2021).

The use of traditional medicines is widely used by the community and is expected to help in handling diseases effectively and efficiently. Traditional medicine is medicine derived from plants, animals, minerals, or a mixture of these ingredients that have been processed simply and can be used as traditional medicine. The use of traditional medicinal plants has been used for generations by the Indonesian people to prevent and treat various diseases. The content of phytochemical compounds is a compound that plays a role in its activity that is beneficial to human health (Batubara and Prasetya., 2020). Some traditional medicines have been widely used empirically for the treatment of erectile dysfunction, including bitter melon and areca nut.

Bitter melon and areca nuts are known to have aphrodisiac effects. The combination of the two will increase libido. Previous research states that the aphrodisiac effect arises allegedly because the active compounds contained in bitter melon, namely triterpenoids and flavonoids, stimulate the production of testosterone, the hormone responsible for sexual drive (Sarapi, 2015). In addition, research has also been conducted on the aphrodisiac effect of areca nut, where oral administration of areca nut ethanol extract at a dose of 50 mg/kg BW can increase sexual activity in male white rats (Parisa, 2019). An aphrodisiac effect is observed when male mice with ICC (Introduction, Climbing, and Citus) are given a combination of bitter melon fruit extract (*Momordica charantia* L.) and white onions (*Allium sativum* L.). Extract bitter melon (*Momordica charantia* L.) and garlic (*Allium sativum* L.), which are known to have an the greatest aphrodisiac effect, at a 1:1 combination dosage concentration (1960/kgBW : 300mg/kgBW) (Alfiraza et al.., 2022).

The prevalence of erectile dysfunction sufferers spread throughout the world is quite high, so for alternative treatment, bitter melon and areca nut seeds have the potential to be used as herbal medicines to treat erectile dysfunction. Currently, herbal medicines derived from nature are believed by the public to be safer to consume than chemical drugs given by doctors, but it should be noted that taking herbal medicines does not guarantee to avoid other unwanted effects. Based on the results of research reported by Mayasankaravalli et al. (2020), it is said that areca nut seeds (*Areca catechu* L.) have hypotensive properties (lower blood pressure) because areca nut seeds contain flavonoid compounds such as catechins, epicatechins, procyanidins, and quercetin, which can alter angiotensin-inhibiting enzymes that can cause vasoconstriction and increase blood pressure (Mayasankaravalli et al., 2020). Meanwhile, Jandari et al. (2020) reported that bitter melon (*Momordica charantia* L.) can significantly reduce systolic and diastolic blood pressure in young adults under 50 years of age with short-term use. Bitter melon has also been shown to have antioxidant and anti-obesity activities (Jandari et al., 2020).

Nowadays, herbal medicines derived from nature are believed by the public to be safer to consume than chemical drugs given by doctors, but it should be noted that taking herbal medicines does not guarantee to avoid unwanted side effects. Herbal medicines may have side effects that are not yet known. From the results of the literature studies that have been conducted, no research has been found on the side effects of using bitter melon extract and areca nut extract together, including the effect of the aphrodisiac activity of a mixture of areca nut extract and bitter melon fruit on blood pressure and body weight, because the use of aphrodisiacs must not only have an optimal effect but also provide a sense of safety and comfort for users and not cause worrying side effects. Based on the above background, the authors are interested in conducting this study, which aims to determine whether the use of bitter melon and areca nut seeds as aphrodisiac agents can affect the blood pressure and body weight of Wistar male white rats.

METHODS

Material

The chemicals used in this study were bitter melon fruit and areca nut seeds obtained from Beringharjo Market, Yogyakarta, CMC. Na 0.5 % b/v (Sigma Aldrich), X-gra® (Phapros), 70 % ethanol (Sigma Aldrich). The test animals used in each experimental group were 5 male white rats, 4 treatment groups, and 1 control group, so the total number of test animals was 25 rats (*Rattus norvegicus* L.).

Tools

Rat cages, macerator, scales, rotary evaporator

(LAB Tech), waterbath, 1 mL oral syringe, glassware, rat *water* bottle, laptop, non-invasive blood pressure monitor (CODA®, Kent Scientific, USA), cloth, and infrared thermometer.

Preparation of Ethanol Extract of Bitter Melon Fruit and Areca Nut Seed

The extraction of bitter melon and areca nut seeds was carried out by the maceration method. A total of 500 grams of areca nut powder and 720 grams of dried bitter melon dry powder were soaked with 70 % ethanol solvent in a macerator. The ethanol extract obtained was then concentrated using a rotary evaporatorwith a temperature setting of 40 °C and continued with the help of a water bath until the extract was obtained. After that, the thick extract was calculated as the percentage of yield against the extracted simplisia.

Dosage Determination of Bitter Melon Fruit and Areca Nut Seed Ethanol Extract

The dose of bitter melon ethanol extract used was 280 mg/kg BW in rats. While the dose of ethanol extract of areca nut seeds used is 50 mg/kg BW of rats. The determination of this dose is based on the results of previous studies related to the effective dose of each extract.

X-Gra® Dosage

X-Gra® was used as a positive control. The usual dose of X-Gra® in humans is 500 mg/60 kg BB, so it is necessary to convert from humans to rats based on the FDA formula. Based on the calculation, the dose of X-Gra® for rats is 10.274 mg/200 kg BB or 51.37 mg/kg BW (Rusdi, 2018).

Each capsule contains Ganoderma lucidum extract 150 mg, Eurycoma radix extract 50 mg, ginseng extract 30 mg, Retrofacti fructus extract 2.5 mg and Royal jelly 5 mg. Ganoderma lucidum extract is able to relieve fatigue and control blood pressure, Eurycoma radix extract plays a very important role in increasing testosterone hormone in men and can increase male vitality because it has aphrodisiacal properties, ginseng extract has an anti-fatigue effect, while Retrofracti fructus and Royal jelly are effective to increase body stamina. X-Gra® is indicated to improve and help overcome erectile dysfunction and premature ejaculation in men. X-Gra® is contraindicated in patients with severe hypertension, prostate cancer and kidney failure (PT Phapros).

Grouping of Test Animals

Group I : CMC Na 0.5 % b/v
Group II : Bitter melon fruit ethanol extract at a dose of 280 mg/kg BW
Group III : Areca nut seed eethanol extract at a dose of 50 mg/kg BW
Group IV : Mixture of Bitter Melon Fruit and Areca Nut seed Ethanol Extract (1:1)
Group V : X-Gra® at a dose of 51.37 mg/kg BB

Blood Pressure Measurement

After administering ethanol extracts of areca nut and bitter melon for 15 consecutive days, blood pressure was measured using a CODA® *non-invasive* blood pressure meter. Observation of experimental animals using the *tail-cuff auto-pickup* method. Measurements were taken before and after treatment. The *non-invasive* blood pressure measurement method was carried out with a tail cuff that was fed a *cuff* containing a *Volume Pressure Recorder* (VPR) *cuff* and *occlusion cuff*. The restraint of rats was carried out in a special place using an *animal holder*. Rat measurements were first warmed to 37 ºC on a *warming pad* until the rat reached the optimum temperature. The occlusion *cuff* uses disposable rubber that is attached first to the rat's tail, followed by a VPR *cuff* as a pulse detector. The *cuff* will automatically inflate upon pressing on the blood-flowed rat, and the blood-flow pulse will be detected. Each measurement was repeated ten times for each experimental animal, and then the average was taken (Stanisavljevic et al., 2022).

Weight Measurement

The allocation of rats into treatment groups consisting of 5 rats each was done randomly. Body weight measurements were taken before and after treatment to determine the changes in body weight that occurred in mice after being treated. Body weight measurements were taken using scales in mice and rats.

Data Analysis

The observation data was analyzed using SPSS 25 software. From the data obtained, preliminary tests were carried out consisting of the Saphiro Wilk Test to determine the normality of the data and the Levene Test for data homogeneity. The data were distributed normally and homogeneously ($p>0.05$), followed by

the one-way Anova parametric test (One Way Anova) and continued with the independent T test if the Anova test results were significant. If the data is not distributed normally, then a non-parametric test of Kruskal Wallis will be carried out and continued with the Mann Whitney Test if the results of the Kruskal Wallis test are significant ($p<0.05$), evidence level 95 %.

RESULTS AND DISCUSSION

Blood Pressure Measurement

The results of blood pressure measurements in normal rats, CMC Na 0.5 % b/v, positive control X-Gra®, bitter melon ethanol extract 280 mg/kg BW, areca nut ethanol extract 50 mg/kg BW, and a combination of bitter melon and areca nut 1:1 can be seen in Table1 and Figure 1. Based on the *Shapiro-Wilk* normality test, the systolic and diastolic blood pressure data were normally distributed (sig<0.05), and based on the *Levene* test, the data were homogeneously distributed (sig<0.05). The data then continued with the statistical test of *two-way* ANOVA parameters. The ANOVA test results showed that neither systolic nor diastolic blood pressure was significantly different. After that, it was continued with the Tukey Test. Based on the Tukey test results, it can be concluded that there is no significant difference between before treatment and after treatment in each group (sig>0.05).

The systolic and diastolic blood pressure pre and post data were homogeneously distributed (sig<0.05) according to the Levene test and normally distributed (sig<0.05) according to the Shapiro-Wilk normality test. After that, the systolic and diastolic blood pressure pre and post data were subjected to a statistical test using the two-way ANOVA settings. The results of the ANOVA test indicated that there was no significant difference between the systolic and diastolic blood pressure (sig>0.05).

The results of this study are not in line with research conducted by Abas in 2015. The results of research conducted by Abas R. *et al. (*2015) oral administration of *Momordica charantia* L. fruit extract (0.5 g/kg BW) for 28 days showed a significant decrease ($p <0.05$) in blood pressure, both systole and diastole. Another study in 47 subjects showed that the use of areca nuts produced an increase in heart rate, regardless of the frequency of use, due to the central sympathetic response, but the effect on blood pressure was more variable, causing a decrease in diastolic pressure due to the presence of peripheral cholinergic effects and an increase in the systolic component (Garg et al., 2014).

In this study, based on the average, each group obtained varying results. In the CMC Na group, areca nut group, and X-Gra group, there was a decrease in blood pressure, both systole and diastole. In the mixed group, there was an increase in blood pressure in both systole and diastole, but in the bitter melon group, there was an increase in systole but a decrease in diastole.

In a study conducted by Widiasari in 2018, it was stated that the ability of flavonoids to regulate blood pressure that has been carried out since several decades ago has been proven effective in suppressing the work of the ACE *enzyme* (*Angiotensin Converting Enzym*) (Widiasari, 2018). Areca seeds are rich in polyphenols and flavonoids, which are the main active compounds (Song et al.., 2022). The results of research by Yang et al. (2012) reported that areca seeds contain flavonoids such as isohamnetin, quercetin, luteolin, and others; besides that, areca seeds also contain tannins, minerals, and vitamins (Allam, 2023). Based on research conducted by Mayasankaravalli et al. (2020), it was reported that areca seeds have the potential to have a hypotensive effect because they contain flavonoid compounds such as *catechin, epicatechin, procyanidin, and quercetin*, which can suppress the activity of ACE (*Angiotensin Converting Enzyme).* Mayasankaravalli's research is reinforced by Song et al.'s research in 2022, which states that areca nut seeds are rich in *natural bioctive*content with antioxidant potential that can inhibit the enzyme that inhibits angiotensin I to angiotensin II, which plays a role in blood pressure regulation (Song et al., 2022).

The biological and pharmacological activities of bitter melon (*Momordica charantia* L.) have been investigated for the last decade. Several studies have shown that bitter melon has beneficial effects on health, including analgesic, anti-inflammatory, anti-viral, antioxidant, anti-cancer, hypoglycemic, hypotensive, and hypocholesterolemic effects (Phimarn et al., 2018; Saad et al., 2017). In studies using rats, bitter melon extract was reported to have a beneficial effect on blood pressure regulation in hypertension model rats (Alam et al., 2015). Oral administration of bitter melon extract in diabetic model rats for 28 days can significantly reduce blood pressure, followed by increased nitric *oxide* (NO) in aortic tissue and *Nitric Oxide Synthase (*NOS) expression in the endothelial wall (Abas et al., 2015).

The mechanism of the hypotensive effect in bitter melon is thought to be inhibiting the Renin Angiotensin Aldosterone (RAA) system in hypertension management. Some bioactive compounds found in bitter melon, especially flavonoids, are reported to inhibit angiotensin-converting enzyme (ACE) activity (Lestari et al., 2017). Bitter melon is rich in phenolic components such as gallic acid, catechin tannins, epicatechin, alkaloids, chlorogenic acid, gentisid acid, rubberonoids, and sterols. Flavonoids exert anti-hypertensive effects through the capture of free radicals and lipid peroxidases (Maaliki et al., 2019). Reactive oxygen species (ROS) production contributes to lowering blood pressure by reducing vascular wall stiffness and preventing vascular aging (Priyanto et al., 2015). Flavonoids can also trigger an increase in NO bioavailability, decrease endothelial oxidative stress, and balance ions that play a role in vascular canals, such as Ca^{2+} activated K^{+} channels (Maaliki, 2019). From the results of the study, it was reported that the use of ethanol extract of areca nut, ethanol extract of bitter melon fruit, and a mixture of ethanol extract of areca nut and bitter melon (1:1) used at effective doses as aphrodisiacs did not cause a decrease or increase in blood pressure in rat test animals, which means it is quite safe to use because it does not cause harmful side effects on blood pressure regulation.

Table 1. Blood Pressure Measurement Results in Rats (mmHg)

Group	*pre*		*post*	
	Mean Systole ± SD	**Mean Diastole ± SD**	**Mean Systole ± SD**	**Mean Diastole ± SD**
CMC Na 0.5% b/v	126.88 ± 43.65	100.29 ± 16.48	103.75 ± 24.01	92.99 ± 12.89
Ethanol extract of bitter melon 280 mg/kg BW	110.79 ± 25.26	110.37± 44.20	118.75 ± 25.16	102.11 ± 17.72
Ethanol extract of areca nut 50 mg/kg BW	129.05 ± 26.21	107.83± 13.09	103.03 ± 21.94 .	91.45 ± 20.13
Ethanol extract of bitter melon: areca nut mixture (1:1)	111.61 ± 12.18	98.43 ± 18.08	117.89 ± 22.49	102.05 ± 20.22
X-Gra®51.37 mg/kg BW	129.70 ± 33.29	115.71 ± 23.62	109.28 ± 26.57	93.89 ± 17.56

a= significant with the control group (group I)
b= significant with X-Gra (group V)

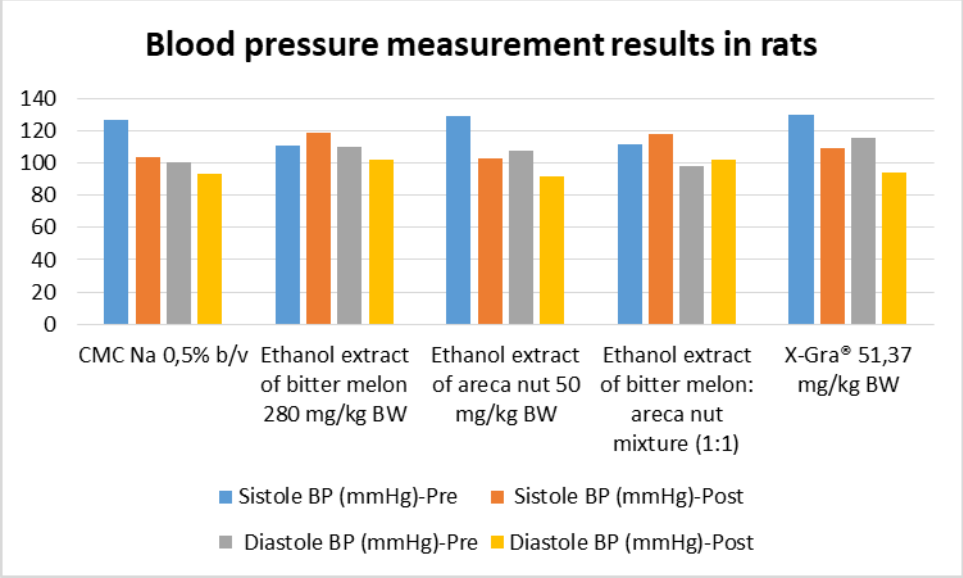

Figure 1. Results of systolic and diastolic blood pressure measurements before and after treatment.

Weight Measurement

The results of body weight measurements in white rats in the normal group CMC Na 0.5 % b/v, positive control X-Gra®, bitter melon ethanol extract 280 mg/kgBB, areca nut ethanol extract 50 mg/kgBB, and a combination of bitter melon ethanol extract and areca nut (1:1) can be seen in Table 2 and Figure 2.

Based on the *Shapiro-Wilk* normality test, the weight data was normally distributed (sig>0.05), and based on the *Levene* test, the data was homogeneously distributed (sig<0.05). The data then continued with the statistical test of *two-way* ANOVA parameters. The ANOVA test results showed the results were not significantly different. After that, it was continued with the Tukey Test. Based on the Tukey test results, body weight shows all data more than 0.05, so it can be concluded that there is no significant difference between pre and post and each formula. The results of this study indicate that bitter melon ethanol extract, areca nut ethanol extract, and a mixture of bitter melon ethanol extract and areca nut 1:1 have no significant effect on body weight in rats.

The results of this study are not in line with research (Reena et al., 2013), which states that the *A. catechu* group showed an increase in body weight of up to 17g. According to Harsa's research in 2019, she obtained the same results as the research conducted, namely that after giving *Momordica charantia L.*, the body weight of male white rats decreased. However, in Harsa's research, the administration of *Momordica charantia L. was* accompanied by a high-fat diet. Areca nut seeds, which are rich in tannins and alkaloids, are one of the plants used in Ayurvedic medicine to treat obesity. Areca nuts are reported to play an important role in fat metabolism and suppress the conversion of carbohydrates into fat (Verma et al., 2014; Sudan et al., 2016). Research conducted by Hsieh et al. (2011) reported that areca nut seed extract containing the active compound arecolin can inhibit the formation of fat droplets in adipocyte tissue, which in turn can suppress the occurrence of obesity (Hieh et al., 2011). This research is reinforced by the research of Bath et al. (2017), which states that hamster test animals given areca nut extract for 4 consecutive months can significantly reduce hamster body weight. In addition to having a blood pressure-lowering effect, bitter melon also provides anti-obesity effects and other metabolite disorders. *In vivo* studies in experimental animals, bitter melon extract prevents weight gain and reduces visceral fat through the mechanism of inducing fatty acid oxidation through up-regulation involving the enzyme *Carnitine Palmitoyl-Transferase-1* (CPT-1), suppressing the process of adipocyte differentiation, and increasing adipocyte cell death through the mediation of *AMP-Activated Protein Kinase* (AMPK) (Ae Yoon et al., 2019).

Based on the results of the study, it was reported that areca nut seed ethanol extract, bitter melon fruit ethanol extract, and a mixture of areca nut and bitter melon ethanol extract (1:1) at their effective doses as aphrodisiacs did not cause changes in the blood pressure of systoles and diastole of male white rats. Areca nut ethanol extract, bitter melon fruit ethanol extract, and a mixture of areca nut and bitter melon ethanol extract (1:1) at their effective doses as aphrodisiacs did not cause any changes in the body weight of male white rats. Areca nut seed ethanol extract, bitter melon fruit ethanol extract, and a mixture of areca nut and bitter melon ethanol extract (1:1) at their effective doses as aphrodisiacs are safe to use because they do not cause harmful side effects on blood pressure and body weight of male white rats.

Table 2: Results of Rat Body Weight Measurement

Group	Average body weight ± SD (g)	
	pre	***post***
CMC Na 0.5% b/v	301.00 ± 32.65	275.00± 39.37
Bitter melon ethanol extract dose of 280 mg/kg BW	314.00 ± 24.37	294.00 ± 50.06
Areca nut ethanol extract dose of 50 mg/kg BW	323.00 ± 32.54	310.00 ± 30.26
Bitter melon:areca nut seed ethanol extract mixture (1:1)	313,00 ± 35.94	315.00 ± 23.20
X-Gra® 51.37 mg/kg BW	311.00 ± 44.73	313.00 ± 30.04

a= significant with the control group (group I)

b= significant with X-Gra (group V)

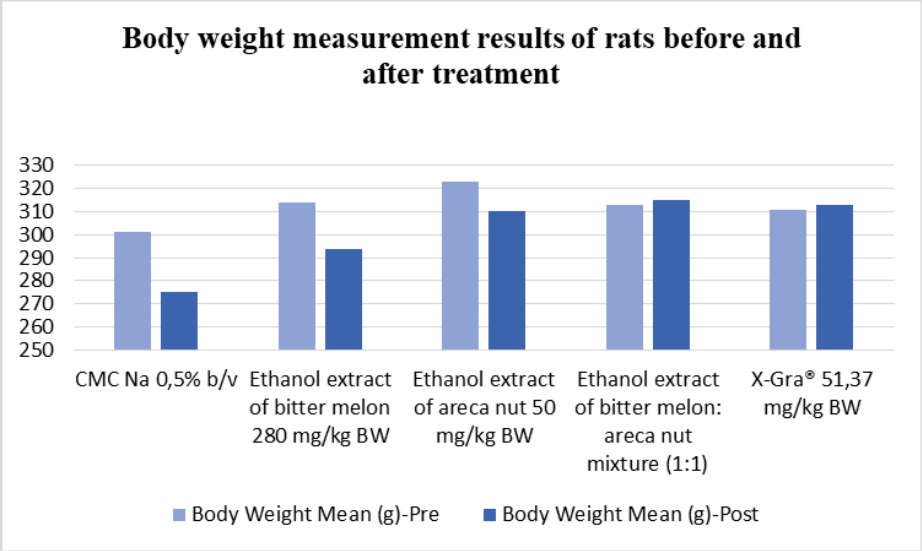

Figure 2. Body weight measurement results of rats before and after treatment.

CONCLUSION

Bitter melon and areca nut seeds ethanol extract as aphrodisiacs have no effect on blood pressure or body weight.

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REFERENCES

Abas, R., Othman, F., &Thent, Z. C. (2015). Effect of Momordica charantia fruit extract on vascular complication in type 1 diabetic rats. *EXCLI journal*, *14*, 179.

Ae Yoon, N.; Park, J.; Yeon Jeong, J.; Rashidova, N.; Ryu, J.; SeobRoh, G.; Joon Kim, H.; Jae Cho, G.; Sung Choi, W.; Hoon Lee, D.; et al. (2019). Anti-obesity Activity of Ethanol Extract from Bitter Melon in Mice Fed High-Fat Diet. Dev. *Reprod.*, 23(2), 129-138.

Ajeigbe, O. F., Ademosun, A. O., & Oboh, G. (2021). Relieving the tension in hypertension: Food–drug interactions and anti-hypertensive mechanisms of food bioactive compounds. *Journal of Food Biochemistry*, *45*(3), e13317.

Alam, M. A.; Uddin, R.; Subhan, N.; Rahman, M. M.; Jain, P.; Reza, H.M. (2015). Beneficial Role of Bitter Melon Supplementation in Obesity and Related Complications in Metabolic Syndrome. *J. Lipids*.

Allam, R., Sahani, G., Raj, A. S., & Mohammed, F. (2023). A phytopharmacological review of the classical Ayurveda drug Puga (*Areca catechu* L.). *Annals of Phytomedicine*, *12*(2), 180-185.

Bhat, S. K., Sarpangala, M., & Ashwin, D. (2017). Antilipidemic activity of arecanut, Areca catechu L.: A valuable herbal medicine. *International Journal of Herbal Medicine*, *5*(1), 35-38.

Batubara, I., & Prastya, M. E. (2020). Potential use of Indonesian medicinal plants for cosmetic and oral health: A review. *Jurnal Kimia Valensi*, *6*(1), 118-132.

Birowo, P., Deswanto, I. A., & Rasyid, N. (2019). Epidemiology of erectile dysfunction: A cross-sectional web-based survey conducted in an Indonesian national referral hospital. *F1000Research*, *8*(817), 817.

Garg, A., Chaturvedi, P., & Gupta, P. C. (2014). A review of the systemic adverse effects of areca nut or betel nut. *Indian journal of medical and paediatric oncology*, *35*(01), 3-9.

Hsieh, T. J., Hsieh, P. C., Wu, M. T., Chang, W. C., Hsiao, P. J., Lin, K. D., Chou, P.C. & Shin, S. J. (2011). Betel nut extract and arecoline block insulin signaling and lipid storage in 3T3-L1 adipocytes. *Cell Biology and Toxicology*, *27*, 397-411.

Indonesia, P.D. H. (2019). Konsensus penatalaksanaan hipertensi 2019. *Indonesian Society Hipertensi Indonesia*, 1-90.

Jandari, S., Ghavami, A., Ziaei, R., Nattagh-Eshtivani, E., Rezaei Kelishadi, M., Sharifi, S., ... & Mohammadi, H. (2020). Effects of Momordica charantia L on blood pressure: a systematic review and meta-analysis of randomized clinical trials. *International Journal of Food Properties*, *23*(1), 1913-1924.

Kessler, A. (2019). The global prevalence of erectile dysfunction: a review. *BJU International*,*124*(4):587-599

Kotta, S., Ansari, S.H., and Ali, J. (2013). Exploring scientifically proven herbal aphrodisiacs. *Pharmacognosy Review*:1-10.

Leisegang, K., & Finelli, R. (2021). Alternative medicine and herbal remedies in the treatment of erectile dysfunction: A systematic review. *Arab journal of urology*, *19*(3), 323-339.

Lestari, P.; Mahayasih, P. G. M. W. (2017). Inhibition Activity of Angiotensin Converting Enzyme (ACE) and Determination of Total Phenolic and Flavonoid Compound from Bitter Melon Leaves (Momordica Charantia L.). *Pharmacogn. J.*, 9(2), 256-26.2.

Maaliki, D.; Shaito, A. A.; Pintus, G.; El-Yazbi, A.; Eid, A. (2019). Flavonoids in Hypertension: A Brief Review of the Underlying Mechanisms. Current opinion in pharmacology. 45, 57-65.

Mayasankaravalli, C., Deepika, K., Lydia, D. E., Agada, R., Thagriki, D., Govindasamy, C., ... & Kim, H. J. (2020). Profiling the phyto-constituents of Punica granatum fruits peel extract and accessing its in-vitro antioxidant, anti-diabetic, anti-obesity, and angiotensin-converting enzyme inhibitory properties. *Saudi Journal of Biological Sciences*, *27*(12), 3228-3234.

Parisa, N., Kamaluddin, M. T., & Salni, S. (2019). Aphrodisiac effects of areca fruit in erectile dysfunction rat model. *Bioscientia Medicina: Journal of Biomedicine and Translational Research*, *3*(3), 16-23.

Park, K., Hwang, E. C., & Kim, S. O. (2011). Prevalence and medical management of erectile dysfunction in Asia. *Asian Journal of Andrology*, *13*(4), 543.

Phimarn, W.; Sungthong, B.; Saramunee, K.; Caichompoo, W. J. P. M (2018). Efficacy of Momordica Charantia L. on Blood Glucose, Blood Lipids, and Body Weight: A Meta-analysis of Randomized Controlled Trials. *Pharmacognosy Magazine*. 14(56), 351.

Priyanto, A. D.; Doerksen, R. J.; Chang, C.-I. Wang-ChouSung, Simon Bambang Widjanarko, Joni Kusnadi, Ya- ChiLin, Ting-ChinWang, Jue-LiangHsu. (2015). Screening, Discovery, and Characterization of angiotensin-I Converting Enzyme Inhibitory Peptides Derived from Proteolytic Hydrolysate of Bitter Melon Seed Proteins. *Journal of proteomics*, 128, 424-435.

Rusdi, N.K., Hikmawanti, N.P.E., Maifitrianti., Ulfah, Y.S., Annisa, A.T. (2018). "Aktivitas Afrodisiaka Fraksi Dari EkstrakEtanol 70 % Daun Katuk (*SauropusAndrogynus* (L). Merr) Pada Tikus Putih Jantan." *Journal Of Pharmaceutical and Research* , 5 (3): 123–32.

Saad, D. Y.; Soliman, M. M.; Baiomy, A. A.; Yassin, M. H.; El-Sawy, H. B (2017). Effects of Karela (Bitter Melon; Momordica Charantia) on Genes of Lipids and Carbohydrates Metabolism in Experimental Hypercholesterolemia: Biochemical, Molecular and Histopathological Study. *BMC Complementary Altern. Med*, 2, 17.

Sarapi, V.A., Bodhi, W., Dan Citraningtyas, G. (2015). Uji EfekAfrodisiakEkstrakEtanolBuah Pare (Momordica Charantia L.) Terhadap Libido Mencit Putih Jantan Galur Wistar (Rattus Norvegicus). *PHARMACON*, 4(3):147-154.

Stanisavljevic, A., Schrader, J. M., Zhu, X., Mattar, J. M., Hanks, A., Xu, F. & Van Nostrand, W. E. (2022). Impact of Non-pharmacological Chronic Hypertension on a Transgenic Rat Model of Cerebral Amyloid Angiopathy. *Frontiers in Neuroscience*, *16*, 811371.

Song, F., Tang, M., Wang, H., Zhang, Y., Zhu, K., Chen, X., Chen H & Zhao, X. (2022). UHPLC-MS/MS identification, quantification of flavonoid compounds from Areca catechu L. extracts and in vitro evaluation of antioxidant and key enzyme inhibition properties involved in hyperglycemia and hypertension. *Industrial Crops and Products*, *189*, 115787.

Sudan, P., Jain, U. K., Sharma, S., & Kaur, R. (2016). A critical insight into the role of herbal drugs in obesity. *World Journal of pharmacological research and technology*, *4*(2), 59-69.

Verma, R. K., & Paraidathathu, T. (2014). Herbal medicines used in the traditional Indian medicinal system as a therapeutic treatment option for overweight and obesity management: A review. *Int J Pharm Sci*, *6*(2), 40-47.

Widiasari S., 2018. MekanismeInhibisi*Angiotensin Converting Enzym Flavonoid* Pada Hipertensi. *Collaborative Medical Journal (CMJ) Vol 1 No 2 Mei 2018*. Departemen Biomedik, Fakultas Kedokteran dan Ilmu Kesehatan, Universitas Abdurrab, Pekanbaru, Riau, Indonesia 2892.

Yang, W. Q., Wang, H. C., Wang, W. J., Wang, Y., Zhang, X. Q., & Ye, W. C. (2012). Chemical constituents from the fruits of Areca catechu. *Zhong Yao Cai= Zhongyaocai= Journal of Chinese Medicinal Materials*, *35*(3), 400-403.