JOURNAL LA MEDIHEALTICO

VOL. 05, ISSUE 04 (880-889), 2024
DOI: 10.37899/journallamedihealtico.v5i4.1556

Combination of Moderate Intensity Exercise and Rose Petals Yoghurt Alters Blood Pressure and Soluble Rage Level in High Advanced Glycation End Products Diet Induced Wistar Rat

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Article Info
Article history:
Received 25 July 2024
Received in revised form 20 August 2024
Accepted 30 September 2024

Keywords:
Hypertension
Rose Petal Yogurt
Moderate Intensity Exercise
sRAGE

Abstract

A diet high in advanced glycation end products (AGEs) has been linked to an increased risk of hypertension and other vascular degenerative diseases. Some intervention such as moderate intensity exercise, yogurt probiotic intake and anthocyanin supplementation had been conducted separately, and showed promising effects. The aim of this study is to analyse the effect of combining rose petal yoghurt and moderate intensity exercise in lowering blood pressure and sRAGE level in high AGEs diet induced model. This research was experimental study, using post test-only control group design. The animals that were used were white male rats (Rattus norvegicus) Wistar strain, divided into 5 groups. Group KN was given standar diet, KP was treated with high AGEs diet, KA was treated with high AGEs diet and combination of rose yoghurt and moderate exercise, KB was given high AGEs diet dan rose yoghurt, and KC group was treated with high AGEs diet and moderate exercise. After 12 weeks systolic and diastolic blood pressure was examined using Kent Scientific CODA blood pressure analyzer and sRAGE examined with ELISA technique. The result shows most decline in systolic and diastolic BP was at KC group which got a high AGEs diet and moderate intensity exercise. KC's systolic BP was measured 120 ± 2.82 mmHg and diastolic at 77.25 ± 9.5 mmHg. The results of ELISA examination show KN has higher sRAGE level at 1865 ± 503.4 ng/L on the contrary KP has lower sRAGE level at 530 ± 78.6 ng/L.

Introduction

The prevalence of hypertension and its association with dietary advanced glycation end products (AGEs) has been a significant focus of recent research. Hypertension remains a major global health challenge, contributing to various diseases and disabilities (Mirmiran et al., 2018). A diet high in advanced glycation end products (AGEs) has been linked to an increased risk of hypertension and other degenerative diseases. AGEs are formed through non enzymatic reactions between sugars and proteins, both endogenously and during the cooking and processing of food, and are ingested through the diet (Ratna et al., 2018). The mechanisms by which AGEs contribute to hypertension include promoting oxidative stress, inflammation, and endothelial dysfunction, which are critical factors in the pathophysiology of cardiovascular diseases. AGEs cause vascular dysfunction by cross-linking extracellular matrix proteins, leading to blood vessel stiffness and cardiac fibrosis, and by reducing nitric oxide bioavailability, which is essential for vascular health (Yubero-Serrano & Pérez-Martínez, 2020). Additionally, insulin resistance, a common feature in hypertension and atherosclerosis, is exacerbated by AGEs. Yogurt consumption has been shown to have a beneficial effect on blood pressure. This antihypertensive effect of yogurt is further supported by research on spontaneously hypertensive rats, where probiotic yogurt significantly reduced blood pressure and improved heart function. The study highlighted that these benefits were mediated through the remodeling of gut microbiota, increasing the abundance of short-chain fatty acid (SCFA)-producing bacteria, which are known to have beneficial effects on cardiovascular health (Kong et al., 2021). Based on that study, it suggests that regular consumption of yogurt, especially probiotic varieties, can contribute to lower blood pressure and potentially reduce the risk of hypertension (Qi et al., 2020).

Anthocyanins, a class of flavonoids found in various fruits and vegetables, have shown significant potential in inhibiting the formation of advanced glycation end products (AGEs), which are implicated in the degenerative diseases. Cyanidin-3-rutinoside (C3R), a specific anthocyanin, has been demonstrated to inhibit methylglyoxal (MG)-induced protein glycation and oxidative damage to proteins and DNA by scavenging free radicals and trapping MG (Sivamaruthi et al., 2018). These effects are mediated through the inactivation of NFκB and MAPK signaling pathways, suggesting a protective role against AGE-mediated inflammation (Nurdjanah et al., 2019). Anthocyanins are vital pigments responsible for the red, purple, and blue colors in rose petals. Epidemiological evidence suggests that moderate consumption of anthocyanins is associated with a reduced risk of atherosclerosis and cardiovascular diseases, further highlighting their therapeutic potential. Thus, anthocyanins from rose petals offer substantial health benefits by mitigating inflammation and its related complications (Bhatt et al., 2021).

Physical exercise also has a multifaceted impact on advanced glycation end products (AGEs), which are implicated in various chronic diseases, including cardiovascular diseases (CVD) and diabetes. Regular physical activity is shown to reduce AGE levels by improving insulin sensitivity, reducing fat mass, inflammation, and the expression of the receptor for AGEs (RAGE), thereby enhancing glucose metabolism and glycemic control (Hooshiar et al., 2022). Exercise also exerts anti-inflammatory effects, as evidenced by a significant reduction in pro-inflammatory cytokines and a decrease in soluble RAGE (sRAGE) levels (Drosatos et al., 2021). These findings underscore the beneficial role of physical exercise in reducing AGEs and modulating sRAGEs, thereby potentially mitigating inflammation and lowering the risk of chronic diseases associated with high AGE levels (Sponder et al., 2018).

Although many studies have been conducted to analyse the antiglycation effect of probiotic, anthocyanin and exercise separately, there is still lack of information about the combination effect. The aim of this recent study is to analyse the effect of combining rose petal yoghurt and moderate intensity exercise in lowering blood pressure and sRAGE level in high AGEs diet induced model.

Methods

Subject

This research was experimental study, using post test-only control group design. The animals that were used were white male rats (Rattus norvegicus) Wistar strain, 10-12 weeks of age with 150-180 grams baseline weight. The animals obtained from the Biomedical Laboratory of Muhammadiyah University of Malang. There were 25 rats as samples. The rats were placed in individual cages in a well-ventilated room with sufficient lighting, where the light-dark cycle was set every 12 hours. Its room temperature ranged from 20-26°C. The cages were cleaned regularly and the husks were replaced every day. After the rats were adapted for one week in a research environment and introduced to the treadmill, they gradually started at 5-15 minutes/ day then divided into five groups with 5 rats each group that were selected randomly. Group

ISSN 2721-1215 (Print), ISSN 2721-1231 (Online)

KN was given standar diet, KP was treated with high AGEs diet, KA was treated with high AGEs diet and combination of rose yoghurt and moderate exercise, KB was given high AGEs diet dan rose yoghurt, and KC group was treated with high AGEs diet and moderate exercise. During the first 8 weeks KP, KA, KB and KC only got a high AGEs diet, and then at 9th weeks they were assessed for the levels of N-Carboxymethyl-lysine (CML) serum in all groups. The blood was collected via sinus orbitalis and assessed using CML ELISA Kit BT Laboratory E1374Ra. When CML level was more than 4,35±0,3 U/mL, 4 groups started getting treatment of rose yoghurt and or moderate exercise as mentioned previously. High AGEs diet made by heating standard pellets consist of 21-23% protein, 5% fat, 40-45% starch, 5% crude fibers, in an oven with temperature of 150oC for 15 minutes (Ratna et al., 2018). Rose yoghurt was given per sonde with volume 3ml and the moderate exercise was given using treadmill with speed 19.3 m/min with 50 incline for 60 min, 5 days/week (Liu et al., 2018). The rose yoghurt and/or moderate exercise treatment were given for 4 weeks until 12th week. At 13th week data was collected.

Rose Petal Yoghurt Preparation

1kg of fresh red rose petals Rosa damascena were shredded and subjected to a temperature of 950C for a duration of 5 minutes using a Thermomix. Afterward, the mixture was cooled to a temperature of 400C and then subjected to pressure in order to extract the juice. The juice was subjected to filtration and passed through a column packed with Amberlite XAD-16 resin. The impurities were removed by rinsing with distilled water, while the phenolic components were extracted using 80% ethanol. The eluate was subjected to vacuum evaporation at a temperature of 400 C. The solvent was removed by evaporation using a Rotavapor (Unipan, Warsaw, Poland) and the resulting substance was freeze-dried (Alpha 1–4 LSC, Christ, Germany), resulting in the manufacture of a dry extract that was utilized as an addition in yogurt production.

The yoghurt was produced using commercially pasteurized milk with a fat level of 3.2%. The dry matter content of milk was augmented by 2% through the use of skimmed milk powder and subjecting it to heat treatment at a temperature of 900C for a duration of 10 minutes. The milk was inoculated with R. damascena dry extract at doses of 0.1% and 0.2%. Control yoghurt was exclusively prepared by incorporating skimmed milk powder. A 2% concentration of Yo-flex, a yoghurt culture consisting of Streptococcus thermophilus and Lactobacillus bulgaricus was introduced to the milk. The incubation process was conducted at a temperature range of 44-450C until the pH level reached 4.6-4.7, which took around 4.5 hours. The yoghurt combination was stored at a temperature below 500C prior to being given to subjects (Szołtysik et al., 2020).

Data Collection

Blood pressure is measured using the tail-cuff method with a Kent Scientific CODA blood pressure analyzer. The rat was placed into the holder by grasping its tail. The rat should be in a calm and baseline condition within the holder before the measurement is taken, and should not be stressed by cold or heat. The tail is then inserted into the tail hole in the cuff, the cuff is tightened, and the rat is prepared for measurement (Andika et al., 2022). After collecting data on the systolic and diastolic blood pressure, which were measured three times, the average value of the rat's blood pressure was calculated. The serum level of sRAGE was measured by the Sandwich-ELISA method. We used the ELISA assay kit BT Laboratory E1851Ra. The analysis was carried out according to the kit protocol.

Data Analysis

Data were analyzed statistically. Data normality was tested by the Shapiro-Wilk test. Homogeneity of data was tested by Levene's test. The blood pressure and sRAGE levels were

ISSN 2721-1215 (Print), ISSN 2721-1231 (Online)

tested by ANOVA followed by Tukey HSD Post Hoc test. The significance level used was more than 95% (p-value <0.05).

Result and Discussion

Blood Pressure Profile

Blood pressure measurements with non-invasive methods were carried out at the end of week 4, 8 and 12. The results were differentiated into systolic and diastolic blood pressure as shown in table 1.

Table 1. Systolic and Diastolic blood pressure profile

Groups	***n***	**Blood Pressure (MmHg)**	**Weeks**		
			4	**8**	**12**
KN	5	Systolic	117.5 ± 4.04	118.25 ± 3.77	119.5 ± 5.26
		Diastolic	71.5 ± 4.12	74.5 ± 5.5	81.5 ± 10.75
KP	5	Systolic	130.75 ± 3.09	142.5 ± 4.12	152.75 ± 3.59
		Diastolic	90.25 ± 2.75	108.75 ± 2.98	116.75 ± 6.29
KA	5	Systolic	132.25 ± 4.35	134.5 ± 4.93	122.75 ± 4.03
		Diastolic	90 ± 2.94	95.5 ± 2.08	80.5 ± 7.72
KB	5	Systolic	132.75 ± 2.06	135.5 ± 4.5	123.75 ± 3.69
		Diastolic	91.5 ± 6.86	96.25 ± 7.32	86 ± 8.44
KC	5	Systolic	134 ± 3.74	134 ± 5.35	120 ± 2.82
		Diastolic	87.5 ± 2.38	93.5 ± 5.67	77.25 ± 9.5

KN: 12 weeks normal diet; KP: 12 weeks high AGES diet; KA: 12 weeks high AGES diet combined with 4 weeks rose yoghurt supplementation and moderate intensity exercise; KB: 12 weeks high AGES diet combined with 4 weeks rose yoghurt suplementation; KC: 12 weeks high AGES diet combined with 4 weeks moderate intensity exercise.

The results of the measurement showed that all groups had increased blood pressure from week 4 to week 8, both of systolic and diastolic BP. At the week 12 KN which only got normal standard diet and KP which given high AGEs diet still had increasing BP, while 3 remaining treatment groups were decline. The most decline systolic and diastolic BP was at KC group which got high AGEs diet and moderate intensity exercise. KC's systolic BP was measured 120 ± 2.82 mmHg and diastolic at 77.25 ± 9.5 mmHg. Based on the results of the ANOVA test for systolic BP there is a significant difference between the averages of 5 groups. where obtained a significance of 0,000. whereas from the post hoc test results there are significant differences between the average of the group KN with KP (p<0.05), whereas KN does not differ meaning with KA, KB and KC (p>0.05). The ANOVA test result for diastolic BP also shows same trend. The study suggested that high-AGEs diet affect blood pressure, while treatment with a combination of rose yoghurt and moderate intensity exercise, giving rose yogurt or moderate intensity exercise alone showed the same effect on blood pressure as normal food consumption.

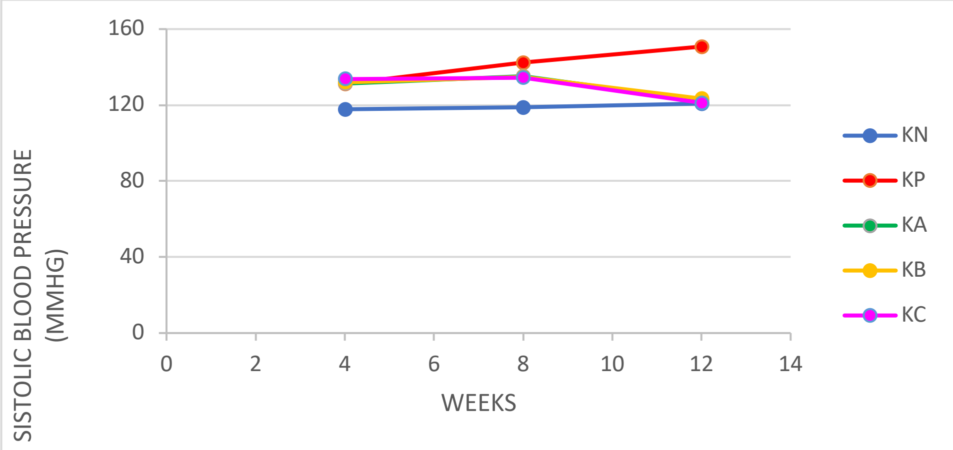

Figure 1. Mean Systolic Blood Pressure from each group

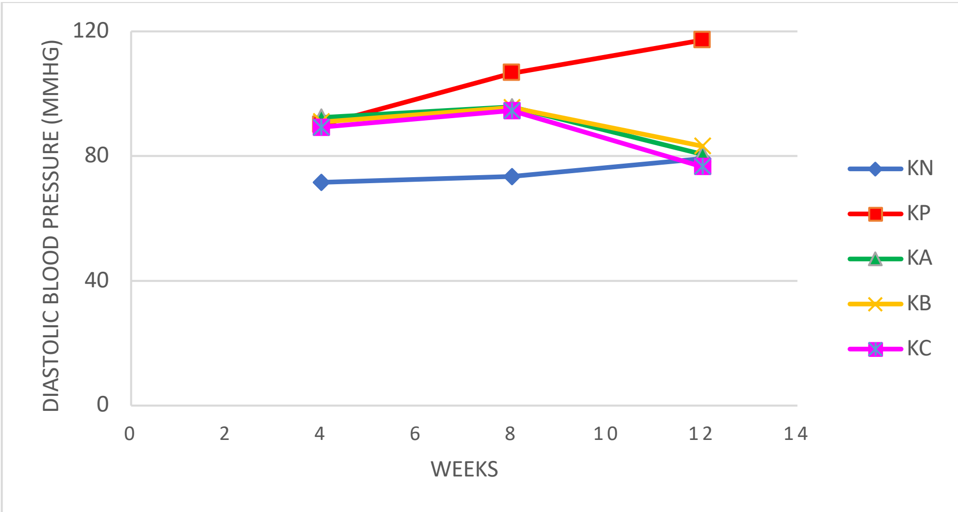

Figure 2. Mean Diastolic Blood Pressure from each group

A high intake of advanced glycation end products (AGEs) has been implicated in the development of hypertension through various mechanisms. AGEs are formed endogenously by non enzymatic reactions between sugars and proteins and are also ingested through diet, particularly from foods cooked using dry-heat methods such as frying and grilling (Yubero-Serrano & Pérez-Martínez, 2020). Studies have shown a strong correlation between high dietary AGE intake and prehypertension, which is a precursor to hypertension, indicating that individuals with higher AGE consumption are at a significantly increased risk of developing hypertension. The mechanisms by which AGEs contribute to hypertension include increased arterial stiffness, inflammation, and oxidative stress, which collectively impaired vascular function and elevate blood pressure (Clifton & Keogh, 2017).

Moderate exercise has been shown to positively affect blood pressure regulation through various mechanisms. Aerobic training, particularly at moderate intensity, is effective in lowering both systolic and diastolic blood pressure in hypertensive patients. This effect is observed across different age groups and irrespective of the duration of hypertension or drug consumption (Mourad et al., 2018). The physiological mechanisms underlying this benefit include the activation of central command and the exercise pressor reflex, which regulate blood flow and blood pressure during physical activity. Specifically, moderate exercise induces vasodilation in active muscles due to metabolite accumulation, while increasing vasoconstriction in inactive tissues through augmented sympathetic outflow (Ramos et al., 2018). Moderate-intensity exercise also enhances endothelial function by increasing nitric oxide (NO) levels and decreasing endothelial microparticles (EMPs), which are markers of endothelial cell activation or apoptosis. This improvement in endothelial function contributes to better vascular health and blood pressure regulation. Furthermore, exercise exerts anti-inflammatory effects through the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis, contributing to its blood pressure-lowering effects (Honda et al., 2021). Studies indicate that moderate-intensity exercise, whether aerobic, resistance, or combined, does not acutely affect flow-mediated dilation (FMD), endothelial progenitor cells (EPCs), endothelial-cell derived microvesicles (EMVs), or oxidative stress markers in hypertensive patients, although it does reduce progenitor cells (PCs) levels regardless of the exercise modality (Waclawovsky et al., 2021).

Yogurt, particularly probiotic and fermented varieties, has been shown to have significant antihypertensive effects through various mechanisms. The fermentation process in yogurt production leads to the release of bioactive peptides, which have been identified to inhibit angiotensin-converting enzyme (ACE), a key player in blood pressure regulation (Sultan et al., 2017). Another critical aspect is the role of gut microbiota in the antihypertensive effects of probiotic yogurt. Studies on spontaneously hypertensive rats (SHR) demonstrated that probiotic yogurt significantly reduced blood pressure and improved heart function by remodeling the gut microbiota, increasing the diversity and abundance of short-chain fatty acid (SCFA)-producing bacteria, which are known to have beneficial effects on cardiovascular health (Kong et al., 2021). While rose anthocyanins, like other anthocyanins, have shown potential in impacting hypertension through various mechanisms. Anthocyanins are flavonoid-derived compounds that can reduce blood pressure by interacting with the Renin-Angiotensin-Aldosterone System (RAAS). Specifically, compounds such as Malvidin have demonstrated strong affinity values for binding to Angiotensin Converting Enzyme (ACE) and Angiotensin II type 1 Receptor (AT1R), which are crucial in blood pressure regulation (Budiarto et al., 2023). Additionally, polyphenols, including anthocyanins from berries, have been shown to enhance endothelial nitric oxide synthase (eNOS) expression and phosphorylation, leading to increased nitric oxide (NO) production, which is vital for endothelial homeostasis and vasodilation (Festa et al., 2021).

This recent study shows no significant differences in blood pressure between groups treated with a combination of rose yogurt and moderate intensity exercise, given only rose yoghurt or given only moderate intensity exercise. Although mean systolic and diastolic BP in KC group which only got moderate intensity exercise is lower than other groups. That finding shows how the body keeps its homeostatic level in order to maintain its physiological function. All the treatment may cause alteration on blood pressure, but the body keeps regulating the homeostatic to obtain normotensive. The body maintains homeostatic blood pressure through a complex interplay of neural reflex controls, feedback mechanisms, and anticipatory regulation processes. Homeostasis, a state of dynamic equilibrium, ensures that internal conditions such as blood pressure remain stable despite external changes. This is achieved through automatic and continuous corrections facilitated by both positive and negative feedback mechanisms (Prabhu, 2023).

Soluble RAGE in serum level

In this study sRAGE level was examined with sandwich ELISA technique. Samples were obtained from blood that were collected from sinus orbitalis at the end of 12th week. The results of ELISA examination show KN has higher sRAGE level at 1865 ± 503.4 ng/L on the contrary KP has lower sRAGE level at 530 ± 78.6 ng/L. Data result of mean sRAGE level shows as graphic at figure 3 below.

ISSN 2721-1215 (Print), ISSN 2721-1231 (Online)

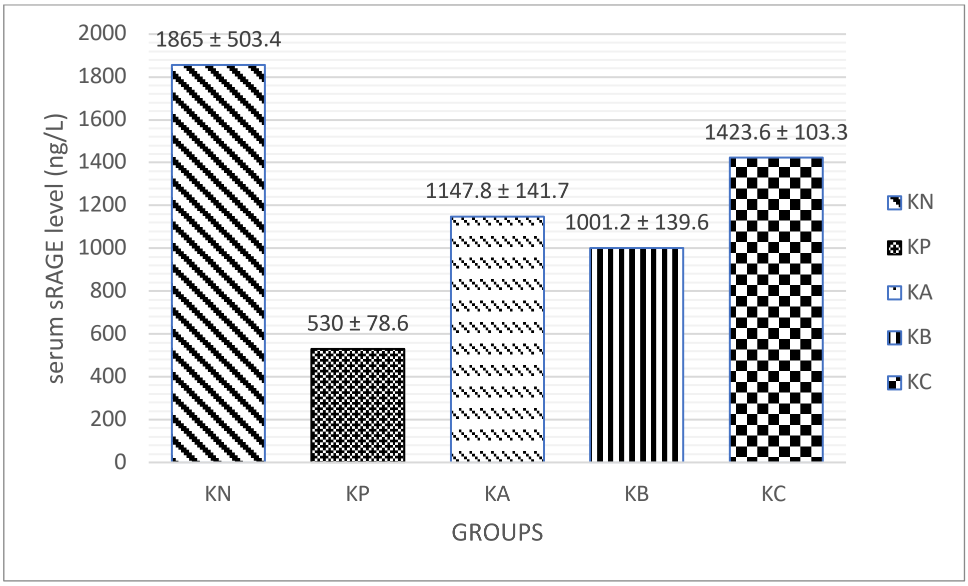

Figure 3. Histogram mean sRAGE level of each group

Higher serum level of sRAGE correlates with lower binding of AGEs to its specific receptor on the cell surfaces (RAGE). Binding on AGEs ligand to its specific receptors will generate an inflammation process that leads to some degenerative process such as vascular degenerative that can cause hypertension. Hence, as in this study induction given as high AGEs diet, all groups that got high AGEs diet show lower sRAGE level than group that got normal diet (KN). This study also found that among all treated groups (KA, KB, KC), the group treated with exercise or KC, has the highest sRAGE level. Results of ANOVA analysis show significant differences among each group ($p < 0,05$). And post hoc analysis shows no significant difference between KN and KC, with p values 0.082. It shows that moderate intensity exercise can affect sRAGE level in subjects with high AGEs intake as the same level with subjects that take a normal diet.

Moderate intensity exercise has been shown to have various physiological impacts, including on markers of oxidative stress and inflammation, which could potentially influence levels of soluble receptors for advanced glycation end-products (sRAGE). sRAGE acts as a decoy receptor, binding to advanced glycation end-products (AGEs) and preventing them from interacting with cell surface receptors that promote inflammation and oxidative stress (Khan et al., 2022). Research indicates that moderate intensity exercise can significantly improve aerobic fitness and cardiovascular health, as demonstrated by a study where participants showed marked improvements in cardiovascular fitness after a 12-week moderate intensity exercise program (Drosatos et al., 2021). Additionally, moderate intensity exercise has been associated with a reduction in oxidative DNA damage, as evidenced by a significant decrease in 8-OHdG levels in older women participating in a moderate intensity resistance training program (Hooshiar et al., 2022). This reduction in oxidative stress markers suggests that moderate intensity exercise could potentially lower systemic inflammation, which might influence sRAGE levels. Furthermore, the relationship between exercise intensity and perceived exertion (SRPE) indicates that moderate intensity exercise is manageable and sustainable for most individuals, which is crucial for long-term adherence and consistent physiological benefits (Khan et al., 2022). Therefore, it is reasonable to infer that moderate intensity exercise could have a beneficial effect on sRAGE levels by reducing oxidative stress and inflammation.

Conclusion

Based on the result and discussion of this study, it can be concluded that combination of rose yogurt intake and moderate intensity exercise can reduce blood pressure in hypertension and also increase sRAGE serum level in the high AGEs diet treated subject. But the effect is not significantly different with subjects that treated with rose yogurt or moderate intensity exercise separately. In order to get a better understanding of the mechanism, it is suggested to perform more pathway analysis and biomolecular assay in the future study.

Acknowledgment

During this study, we would like to thank the Biomedical laboratory of the Faculty of Medicine, Muhammadiyah University of Malang, for the help conducting the research. All research funding was from an internal research grant Faculty of Sport Science, State University of Malang.

References

Andika, M., Humaira, V., & Yesika, R. (2022). Effects of Bisoprolol on Decreased Blood Pressure of Systole in Male White Rats Hypertension and Hypertension with Complications of Liver Dysfunction. *Int. J. Pharm. Sci. Med, 7*, 1–6. https://doi.org/10.47760/ijpsm.2022.v07i02.001

Bhatt, N., Waly, M. I., & Ali, A. (2021). Anti-inflammatory role of anthocyanins in the prevention of hyperhomocysteinemia-mediated cardiometabolic diseases. *Nutritional Management and Metabolic Aspects of Hyperhomocysteinemia*, 33–49. https://doi.org/10.1007/978-3-030-57839-8_3

Budiarto, D., Wijianto, B., & Hariyanto, I. H. (2023). Study of anthocyanin molecule blocking as anti-hypertensive through the pathway of the renin-angiotensin-aldosterone system (RAAS). *Indonesian Journal of Chemical Research, 11*(1), 49–58. https://doi.org/10.30598//ijcr.2023.11-bud

Clifton, P., & Keogh, J. (2017). Role of dietary advanced glycation end products. *Current Opinion in Lipidology, 28*(6), 514–515. https://doi.org/10.1097/MOL.0000000000000452

Drosatos, I.-A., Tsoporis, J. N., Izhar, S., Gupta, S., Tsirebolos, G., Sakadakis, E., Triantafyllis, A. S., Rigopoulos, A., Rigopoulos, D., & Rallidis, L. S. (2021). Differential regulation of circulating soluble receptor for advanced glycation end products (sRAGEs) and its ligands S100a8/A9 four weeks post an exercise intervention in a cohort of young army recruits. *Biomolecules, 11*(9), 1354. https://doi.org/10.3390/biom11091354

Festa, J., Da Boit, M., Hussain, A., & Singh, H. (2021). Potential benefits of berry anthocyanins on vascular function. *Molecular Nutrition & Food Research, 65*(19), 2100170. https://doi.org/10.1002/mnfr.202100170

Honda, H., Igaki, M., Komatsu, M., & Tanaka, S. (2021). Effect of moderate-intensity seated exercise on the management of metabolic outcomes in hypertensive individuals with or without exercise habits. *Journal of Exercise Science & Fitness, 19*(1), 51–56. https://doi.org/10.1016/j.jesf.2020.09.002

Hooshiar, S. H., Esmaili, H., Taherian, A., & Jafarnejad, S. (2022). Exercise, advanced glycation end products, and their effects on cardiovascular disorders: a narrative review. *Heart and Mind, 6*(3), 139–150. https://doi.org/10.4103/hm.hm_31_22

Khan, A., Shaikh, A. H., Butt, M. Z. I., Jamil, M., Khan, A., Soomro, J. A., Khan, M., Selamoglu, Z., Ozdemir, B., & Khan, A. M. (2022). Assessment of Aerobic Fitness Associated with Moderate Intensity Exercise: Aerobic Fitness Associated with Moderate Intensity Exercise. *Pakistan Journal of Health Sciences*, 249–252. https://doi.org/10.54393/pjhs.v3i05.253

Kong, C.-Y., Li, Z.-M., Mao, Y.-Q., Chen, H.-L., Hu, W., Han, B., & Wang, L.-S. (2021).

Probiotic yogurt blunts the increase of blood pressure in spontaneously hypertensive rats via remodeling of the gut microbiota. *Food & Function, 12*(20), 9773–9783. https://doi.org/10.1039/D1FO01836A

Liu, S., Li, Z., Xu, S., Xu, L., Yang, M., & Ni, G. (2018). Intensity-dependent effect of treadmill running on differentiation of rat bone marrow stromal cells. *Molecular Medicine Reports, 17*(6), 7746–7756. https://doi.org/10.3892/mmr.2018.8797

Mirmiran, P., Yousefi, R., Mottaghi, A., & Azizi, F. (2018). Advanced glycation end products and risk of hypertension in Iranian adults: Tehran lipid and glucose study. *Journal of Research in Medical Sciences, 23*(1), 43. Https://doi.org/10.4103/jrms.JRMS_982_17

Mourad, M. B., Sabira, F., Azeddine, R., & Khaled, B. (2018). The Importance Of Moderate-Intensity Aerobic Sports Activities In Lowering The Level Of High Blood Pressure For Patients. *European Journal of Physical Education and Sport Science*. http://dx.doi.org/10.46827/ejpe.v0i0.1469

Nurdjanah, S., Yuliana, N., Aprisia, D., & Rangga, A. (2019). PENGHAMBATAN AKTIVITAS ENZIM α-GLUKOSIDASE OLEH EKSTRAK KASAR ANTOSIANIN UBI JALAR UNGU SEGAR DAN PRODUK OLAHANNYA (inhibition activity of α-glucosidase by anthocyanin crude extract from purple sweet potato and its products). *Biopropal Industry, 10*(2), 83–94. https://doi.org/10.36974/jbi.v10i2.4765

Prabhu, S. R. (2023). Homeostasis. *In Textbook of General Pathology for Dental Students* (pp. 5–10). Springer.

Qi, D., Nie, X.-L., & Zhang, J.-J. (2020). The effect of probiotics supplementation on blood pressure: a systemic review and meta-analysis. *Lipids in Health and Disease*, 19, 1–11. https://doi.org/10.1186/s12944-020-01259-x

Ramos, R. M., Coelho-Júnior, H. J., Prado, R. C. R. do, da Silva, R. S., Asano, R. Y., Prestes, J., Medeiros, A. I. A., Rodrigues, B., & Assumpção, C. de O. (2018). Moderate aerobic training decreases blood pressure but no other cardiovascular risk factors in hypertensive overweight/obese elderly patients. *Gerontology and Geriatric Medicine, 4*, 2333721418808645. https://doi.org/10.1177/2333721418808645

Ratna, A. P., Soeharto, S., Falyani, S. A., & Batmomolin, P. B. (2018). Rosella Flower Extract Prevent Increasing of Interleukin-6 and Amyloid-β Levels in Brain Tissue of Heated Diet-Treated Rats. *The Journal of Experimental Life Science, 8*(2), 119–125. https://doi.org/10.21776/ub.jels.2018.008.02.09

Sivamaruthi, B. S., Kesika, P., Subasankari, K., & Chaiyasut, C. (2018). Beneficial effects of anthocyanins against diabetes mellitus associated consequences-A mini review. *Asian Pacific Journal of Tropical Biomedicine, 8*(10), 471–477. https://doi.org/10.4103/2221-1691.244137

Sponder, M., Campean, I.-A., Emich, M., Fritzer-Szekeres, M., Litschauer, B., Graf, S., Dalos, D., & Strametz-Juranek, J. (2018). Long-term physical activity leads to a significant increase in serum sRAGE levels: a sign of decreased AGE-mediated inflammation due to physical activity? *Heart and Vessels, 33,* 893–900. https://doi.org/10.1007/s00380-018-1125-5

Sultan, S., Huma, N., Butt, M. S., & Shahid, M. (2017). Antihypertensive and antioxidative potential of water soluble peptide fraction from different yoghurts. *Journal of Food Processing and Preservation, 41*(3), e12979. https://doi.org/10.1111/jfpp.12979

Szołtysik, M., Kucharska, A. Z., Sokół-Łętowska, A., Dąbrowska, A., Bobak, Ł., &

Chrzanowska, J. (2020). The effect of Rosa spinosissima fruits extract on lactic acid bacteria growth and other yoghurt parameters. *Foods, 9*(9), 1167. https://doi.org/10.3390/foods9091167

Waclawovsky, G., Boll, L. F. C., Eibel, B., Alegretti, A. P., Spagnol, F., De Paoli, J., Wajner, S., Marschner, R. A., Schaun, M. I., & Lehnen, A. M. (2021). Individuals with controlled hypertension show endothelial integrity following a bout of moderate-intensity exercise: Randomized clinical trial. *Scientific Reports, 11*(1), 8528. https://doi.org/10.1038/s41598-021-87990-6

Yubero-Serrano, E. M., & Pérez-Martínez, P. (2020). Advanced glycation end products and their involvement in cardiovascular disease. *In Angiology* (Vol. 71, Issue 8, pp. 698–700). SAGE Publications Sage CA: Los Angeles, CA. https://doi.org/10.1177/0003319720916301

ISSN 2721-1215 (Print), ISSN 2721-1231 (Online)