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Short-term effect of apple vinegar on blood pressure, pulse pressure, and heart rate in healthy people: Randomized clinical trial- a linear mixed model analysis

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Abstract

Background and objective: Apple vinegar is a fermented product prescribed for hypertension in Persian medicine. This study aimed to evaluate the short-term effect of oral administration of apple vinegar on systolic and diastolic blood pressure, pulse pressure, and heart rate in healthy individuals.

Materials and methods: This study was conducted on 40 healthy people. On test day, control group drank 200 ml water 4 h after breakfast, while test groups drank 200 ml water containing 22, 28, and 34 g apple vinegar. Blood pressure was measured just before intervention and also after intervention every 15 min for 2 h. Heart rate measurement was done before and after intervention. Pulse pressure was calculated as difference of systolic and diastolic blood pressures every time.

Results and conclusion: Our results showed no significant relationship between consumption of apple vinegar and systolic blood pressure. In the test group administered 22 g apple vinegar, pulse pressure and diastolic blood pressure decreased significantly after 75 min. According to linear mixed model, changes in systolic blood pressure score were not significantly affected by groups, but it was significantly affected by time ($p = 0.037$). In addition, interaction of time and low-dose apple vinegar group for diastolic blood pressure and pulse pressure were significant ($p = 0.005$ and $p = 0.008$, respectively). Higher amounts of apple vinegar showed no significant effect. This study revealed that apple vinegar could decrease diastolic blood pressure and pulse pressure in healthy people in short-term use. Considering there is no side-effect for apple vinegar by the studied amounts and also its potential in modulation of blood pressure, evaluation of its effects in hypertensive patients is recommended for further studies.

Keywords: Apple vinegar, blood pressure, heart rate, Persian medicine, pulse pressure

1. Introduction

Hypertension is a chronic disease affects 20-35% of adults in the world. It is one of the risk factors affecting morbidity and mortality rates in developing countries such as Iran. Importantly, number of undiagnosed, untreated, and uncon-

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trolled hypertensive patients in middle-income countries is higher than high-income countries, possibly due to weak health systems [1].

Unhealthy diet and inappropriate lifestyle are effective factors in development of hypertension [2]. The both factors are focused in Persian medicine (Iranian traditional medicine), for maintenance of health and treatment of diseases such as hypertension [3,4]. According to ancient Persian medicine, Imtela is a disease with manifestation similar to what is known as hypertension currently. In Persian medicine, one of treatments in management of Imtela (hypertension) is daily intake of vinegar (Serkeh), which was prescribed by *Al-Akhawayni* (the writer of *Hidāyat al-Muta'allimin fi al-Tibb*). Furthermore, he recommended managing anger, intake of reduced volume of meal, using low energy foods, and no intake of wine, meat, and pastries [5].

Acetic acid is the main ingredient of vinegar. In the past, vinegar was produced from different sources of carbohydrate-rich foods including date, sugar, honey, cereals, and watery sweet fruits (such as grape, apple, quince, and pear) [6-8]. Vinegar and its components have antioxidant and antitumor activity and are effective in treatment of infections, modulation of lipid profile, weight loss, control of diabetes, treatment of injuries, reduction of high blood pressure in hypertensive patients, and to keep the nervous system healthy [9]. Despite several short- and long-term animal studies about the effects of vinegar [10-13], most of clinical studies have been followed up in long-term [2,14-17]. Therefore, the current work aimed to study short-term effect of apple vinegar (AV) on systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure (PP), and heart rate (HR) in healthy subjects.

2. Materials and methods

2.1. Subjects

The participants were 40 healthy volunteers aged 20-60 years. Inclusion criteria were included to no history of allergy to AV, no digestive problems such as reflux, no smoking, and body mass index between 18.5 and 29.9 kg/m^2. Exclusion criterion was unwillingness of the individuals to cooperate with the study. In order to control and minimize the possible effects of diet on blood pressure, they were requested to follow the nutritionist's recommendations one week before the intervention. The subjects were provided with the informed consent form before the study. Flow diagram of the study is presented in Figure 1.

2.2. Preparation of apple vinegar

AV was purchased from a natural products store in Qazvin and its acidity was determined in the laboratory. Then, the acidity was adjusted to 5%. Amounts of 22, 28, and 34 g of the adjusted AV were made up to 200 ml by water. The final AV samples were considered as low-dose, moderate-dose, and high-dose, respectively.

2.3. Study design

This study is a pilot randomized clinical trial registered in the Iranian Registry of Clinical Trials as IRCT20171203037724N1. It also received ethical approval from the Ethics committee of Guilan University of Medical Sciences (Ethics code: IR.GUMS.REC.1397. 102). The subjects were randomized with random block using random allocation software. Selection sequence was divided into four groups of women (20) and men (20) that were kept in sealed letters in the Cardiovascular Diseases Research Center of Heshmat Hospital in Rasht. They were opened at the start of the study in the morning and closed at night. Based on sex and inclusion criteria for sequencing, the subjects were assigned to one of the four groups. Each group consisted of 10 participants. The groups were control (C), low-dose apple vinegar (LDAV), moderate-dose apple vinegar (MDAV), and high-dose apple vinegar (HDAV). On test day, the control group drank 200 ml water 4 h after breakfast. In comparison, the test groups drank 200 ml AV solutions containing 22, 28, and 34 g adjusted AV under the same condition [18].

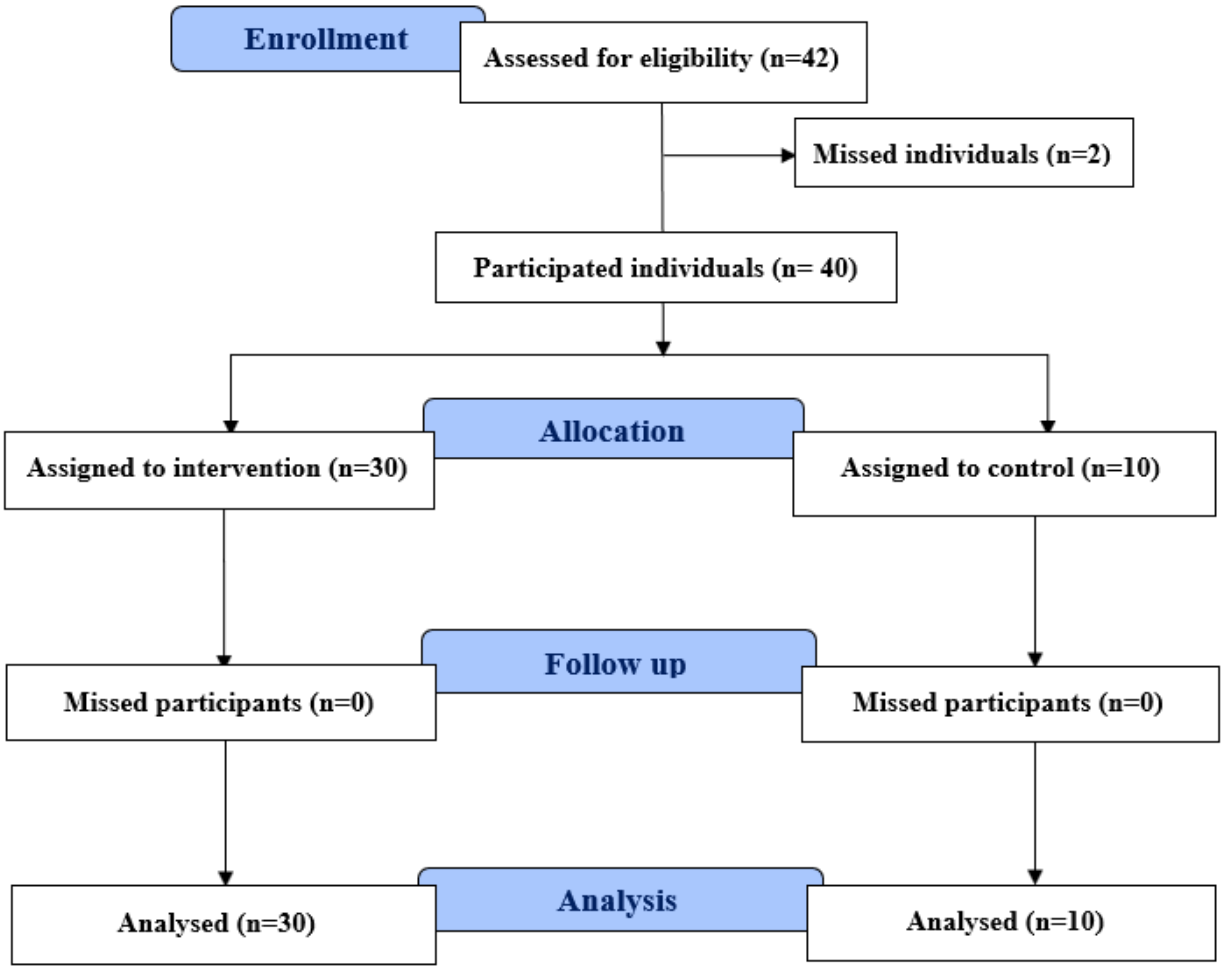

Figure 1- Flow diagram of the study

2.4. Measurements

SBP and DBP were measured before receiving AV and every 15 min after receiving AV for 2 h. PP was calculated as difference of SBP and DBP every time. HR was determined by electro-cardiogram before and after intervention. The procedures were done in the Cardiovascular Research Center of Guilan University of Medical Sciences (Rasht, Iran).

2.5. Statistical analysis

Statistical analyses were performed with SPSS software version 21 (SPSS Inc., Chicago, IL, USA). Linear mixed model (LMM) was used to analyze SBP, DBP, and PP data. Equations of LMM were included to two levels.

Equation in level 1:

$$y_{ij} = b_{0i} + b_{1i}\text{time}_{ij} + e_{ij}$$

Equation in level 2:

$$b_{0i} = \beta_{00} + \beta_{01}\text{group} + \upsilon_{0i}$$

$$b_{1i} = \beta_{10} + \beta_{11}\text{group}$$

Where, y_{ij} represents SBP, DBP, and PP of the individuals at time j = 0, 15, 30, 45, 60, 75, 90, 105, and 120 min. In level 1, time is included as covariate and b_{1i} indicates each individual's response during time. The individual's response

at baseline (b_{0i}) may be differ by its random effect in level 2 (υ_{0i}). In level 2, the regression coefficient β_{01} represents that each participants' initial status (intercept) will be associated with their covariates. The regression coefficient β_{11} indicates interaction of time and the covariates. It shows that impact of time (b_{1i}) on the outcome will be associated with their covariates. On the other hand, changes in SBP, DBP, and PP scores (under time effect) are significantly different between subgroups when a significant interaction exists.

According to the equations, we adjusted the effects of time and group, two-way interaction of time and group as well as random effects of the intercept (baseline score). Bayesian information criteria (BIC) was used to find the best fit showing the least value and autoregressive of order 1 was selected. Parameters were estimated by the method of restricted maximum likelihood (REML). To compare the data, ANOVA followed by Tukey test were used. Differences were considered significant at $p \leq 0.05$.

3. Results and discussion

From October 2018 to January 2019, 42 volunteers announced their consent for participation in our study, of which two individuals were missed further due to personal issues (Figure 1). Demographic information of the participants is presented in Table 1. As seen, demographic and clinical data are similar among groups.

Table 1- Demographic and clinical information of the subjects

*Data are presented as mean ±standard deviation. HDAV: high dose apple vinegar; MDAV: moderate dose apple vinegar; LDAV: low dose apple vinegar; C: control; BMI: Body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; PP: pulse pressure.

	Group				
	HDAV	MDAV	LDAV	C	p-value
Men/Women	5/5	5/5	5/5	5/5	0.999
Age (year)	25.3 ±3.7	24.5 ±2.1	28.6 ±10.7	26.4 ±3.7	0.691
BMI (kg/m^2)	24.9 ±2.7	25.5±3.8	23.4±2.9	23.0±4.0	0.311
SBP (mmHg)	120.7±9.1	118.8±8.0	118.1±8.9	118.5±11.6	0.932
DBP (mmHg)	71.5±5.5	73.7±6.1	72.1±7.5	70.7±9.5	0.827
HR (beats/min)	72.7±10.4	71.3±8.2	78.5±10.8	80.0±10.9	0.398
PP (mmHg)	87.9±6.0	88.7±6.4	87.4±7.4	86.6±9.6	0.938

Changes of SBP, DBP, and PP scales during 120 min after intervention are presented in Table 2 and Figure 2. In LDAV group, SBP constantly declined up to 30 min compared to SBP in other groups which showed fluctuation (Figure 2a). No significant changes in SBP were observed before and after intervention in all groups ($p > 0.05$). In agreement, changes of SBP score were not significantly affected by the four groups as subscale, but effect of time was significant ($p = 0.037$) according to LLM data (Table 3). However, interaction of each group with time was not significant for SBP score. For DBP, a sharp decline was observed in the second quarter after intervention (15-30 min) in LDAV group, while it declined mild in other three groups (Figure 2b). Interestingly, change of DBP in LDAV group after 75 min (12.6% reduction) was significantly different from control ($p = 0.01$) (Table 2). Changes of DBP score were not significantly affected by all the subscales (the four groups and time), while DBP was significantly affected by interaction of time and LDAV group ($p = 0.005$) according to LLM data (Table 3). Similar result was observed for PP changes after 75 min and significant difference ($p = 0.03$) was observed between LDAV group and control (Table 2). According to Figure 2C, changes of PP in LDAV group were more regular than the other groups with fluctuation. Changes of PP score were not

significantly affected by all the subscales (the four groups and time), while PP was significantly affected by interaction of time and LDAV group (p = 0.008) according to LLM data (Table 3).

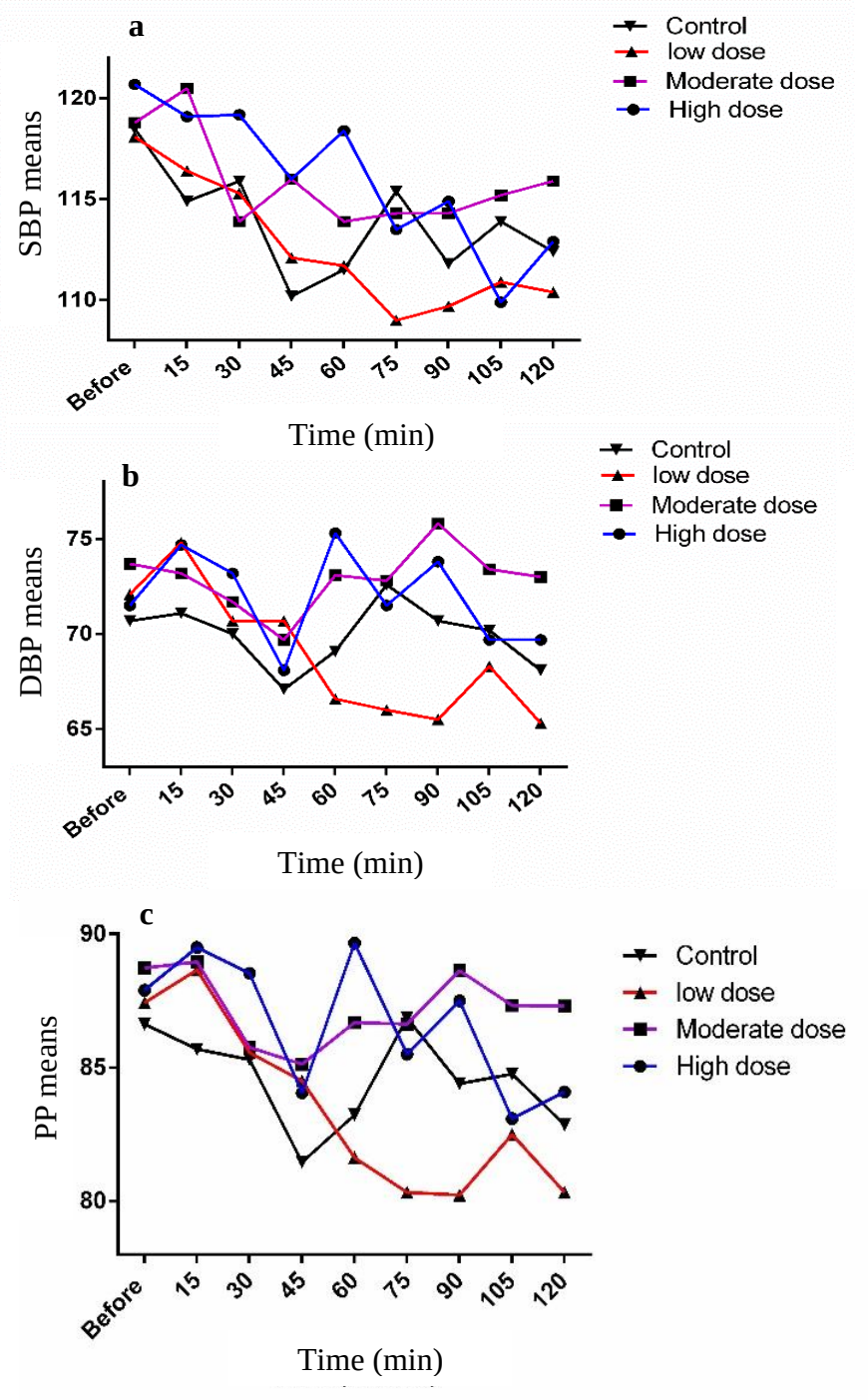

Figure 2- Means of systolic blood pressure, diastolic blood pressure, and pulse pressure in the subjects

Table 2- Changes of SBP, DBP, and PP in AV-treated groups compared to control

Parameter	Group p-value	Time (min)							
		15	30	45	60	75	90	105	120
SBP	HDVA	-1.4±3.1	-0.5±3.9	-2.9±3.2	-3.5±3.9	3.5±3.7	-0.6±3.3	5.2±3.1	1.5±3.2
	p-value	0.9	0.9	0.6	0.7	0.6	0.9	0.2	0.9
	MDAV	-4.0±3.1	2.7±3.9	-4.2±3.2	-0.9±3.9	1.6±3.7	-1.4±3.3	-0.4±3.1	-2.2±3.2
	p-value	0.4	0.8	0.4	0.9	0.9	0.9	0.9	0.8
	LDAV	-1.0±3.1	0.8±3.9	-1.6±3.2	0.09±3.9	5.6±3.7	1.8±3.3	2.6±3.1	1.7±3.2
	p-value	0.9	0.9	0.9	1.0	0.3	0.9	0.7	0.9
DBP	HDVA	-3.0±5.4	-2/0±4.8	0.7±4.3	-7.0±3.5	3.8±4.4	-1.2±6.1	2.4±4.1	-0.8±3.1
	p-value	0.8	0.9	0.9	0.1	0.7	0.9	0.8	0.9
	MDAV	1.8±5.4	2.8±4.8	1.1±4.3	-0.8±3.5	5.1±4.4	-0.8±6.1	0.3±4.1	-2.6±3.1
	p-value	0.9	0.8	0.9	0.9	0.5	0.9	1.0	0.7
	LDAV	-2.4±5.4	2.2±4.8	-2.3±4.3	6.1±3.5	12.6±4.4	11.3±6.1	5.3±4.1	6.3±3.1
	p-value	0.9	0.9	0.9	0.2	0.01*	0.1	0.4	0.1
PP	HDVA	-2.5±3.4	-1.4±3.9	-0.8±3.1	-5.4±3.0	3.6±3.6	-1.1±4.0	3.7±3.3	0.2±2.7
	p-value	0.8	0.9	0.9	0.1	0.6	0.9	0.5	1.0
	MDAV	-1.0±3.4	2.6±3.9	-1.3±3.1	-1.0±3.0	3.3±3.6	-1.4±4.0	-0.05±3.3	-2.5±2.7
	p-value	0.9	0.8	0.9	0.9	0.6	0.9	1.0	0.6
	LDAV	-1.9±3.4	1.6±3.9	-2.0±3.1	3.3±3.0	9.3±3.6	6.8±4.0	4.1±3.3	4.1±2.7
	p-value	0.8	0.9	0.8	0.5	0.03*	0.2	0.4	0.3

*Data are presented as mean ±standard deviation. AV: apple vinegar; HDAV: high dose apple vinegar; MDAV: moderate dose apple vinegar; LDAV: low dose apple vinegar; SBP: systolic blood pressure; DBP: diastolic blood pressure; PP: pulse pressure.

Table 3- Linear mixed model of SBP, DBP, and PP scores

Scales	Subscales and interactions	Estimate	SE	df	t	p-value	95% Confidence Interval	
							Lower Bound	Upper Bound
SBP	Intercept	116.18	2.93	47.290	39.652	0.000	110.29	122.08
	HDAV	4.43	4.14	47.290	1.071	0.290	-3.89	12.77
	MDAV	1.59	4.14	47.290	0.384	0.703	-6.74	9.92
	LDAV	0.61	4.14	47.290	0.147	0.884	-7.72	8.94
	C	0[a]	0					
	T	-0.04	0.017	81.036	-2.117	0.037	-0.072	-0.002
	T * HDAV	-0.037	0.024	81.036	-1.520	0.132	-0.087	0.011
	T * MDAV	0.007	0.024	81.036	0.289	0.773	-0.042	0.056
	T * LDAV	-0.030	0.024	81.036	-1.218	0.227	-0.079	0.019
	T * C	0[a]	0					
DBP	Intercept	70.37	2.32	49.530	30.251	0.000	65.70	75.05
	HDAV	2.72	3.29	49.530	0.829	0.411	-3.88	9.33
	MDAV	1.96	3.29	49.530	0.597	0.553	-4.64	8.57
	LDAV	2.61	3.29	49.530	0.796	0.430	-3.99	9.22
	C	0[a]	0					
	T	-.007	0.015	123.059	-0.472	0.638	-0.036	0.022
	T * HDAV	-0.012	0.021	123.059	-0.582	0.561	-0.054	0.029
	T * MDAV	0.016	0.021	123.059	0.798	0.426	-0.025	0.059
	T * LDAV	-0.061	0.021	123.059	-2.885	0.005	-0.103	-0.019
	T * C	0[a]	0					
PP	Intercept	85.60	2.37	45.588	36.058	0.000	80.82	90.38
	HDAV	3.32	3.35	45.588	0.991	0.327	-3.43	10.08
	MDAV	1.92	3.35	45.588	0.572	0.570	-4.83	8.68
	LDAV	1.94	3.35	45.588	0.578	0.566	-4.81	8.70
	C	0[a]	0					
	T	-0.017	0.013	108.560	-1.282	0.202	-0.043	0.009
	T * HDAV	-0.021	0.018	108.560	-1.133	0.260	-0.058	0.015
	T * MDAV	0.012	0.018	108.560	0.672	0.503	-0.024	0.049
	T * LDAV	-0.050	0.018	108.560	-2.702	0.008	-0.088	-0.013
	T * C	0[a]	0					

[a] It was set to zero because it was redundant. HDAV: high dose apple vinegar; MDAV: moderate dose apple vinegar; LDAV: low dose apple vinegar; C: control; T: time; SBP: systolic blood pressure; DBP: diastolic blood pressure; PP: pulse pressure.

HR changed significantly after intervention in all groups ($p \leq 0.05$). However, no significant change was observed between control and treatments (Table 4).

Table 4- Effect of AV on HR (beats/min) in the objects

Group	Before intervention	After intervention	Changes of HR	p-value
HDAV	73 ±10	63 ±10	10.2 ±11.1	0.01*
MDAV	71 ±8	66 ±10	5.1 ±6.9	0.04*
LDAV	79 ±11	70 ±10	8.3 ±9.5	0.02*
C	80 ±11	70 ±14	9.9 ±13.8	0.05*
p-value	0.17	0.37	0.69	

*****Data are presented as the mean± standard deviation. AV: apple vinegar; HR: heart rate; HDAV: high dose apple vinegar; MDAV: moderate dose apple vinegar; LDAV: low dose apple vinegar; C: control.

The purpose of this study was to examine the short-term effects of AV consumption on BP, PP, and HR in healthy individuals. Our findings showed no significant dose-response relationship for the variables at different times. Modulation of BP is effective factor in prevention of cardio-vascular diseases [19-21]. In this regard, several studies have been reported the association of vinegar with BP reduction [2,10-13,15-17]. Indeed, acetic acid is the active ingredient of vinegar and is responsible for its health benefits such as treatment of hypertension, hyper-lipidemia, and hyperglycemia [11,22,23]. After consumption, acetic acid is converted to acetate in the body [24]. Therefore, functionality of vine-gar depends on adequate absorption of acetate.

Sugiyama et al. reported that acetic acid absorption in subjects drank vinegar was faster than group consumed capsule containing 750 mg acetic acid. In the first group, serum concentration of acetate increased immediately after intake, and reached its maximum after 15 min followed by gradually decrease for 120 min. Although, serum level of acetate exceeded the physiologically active concentrations in both groups [8]. In another study by Sugiyama et al., cardiovascular effects of a beverage containing wine vinegar and grape juice (3 ml/kg) were evaluated in phenobarbital-anesthetized rats every 10 min for 190 min. After administration, HR decreased at 60-120 min, and mean blood pressure decreased at 50-130 min and 150-160 min, while no significant change was observed in electrocardiogram [12]. In agreement, Kondo et al. found that acetic acid can significantly reduce blood pressure and renin activity in hypertensive rats [11]. In addition, Sakakibara et al. examined the impact of acetate on endothelial nitric oxide synthase (eNOS) in human umbilical vein endothelial cells (HUVECs) by immunoblotting assay and studied the ability of acetic acid to upregulate flow-mediated vasodilatation in human. In HUVECs, acetate caused a biphasic increase in phosphorylated form of eNOS. Administration of vinegar (containing 4–5% w/v acetic acid) improved flow-mediated vasodila-tation in postmenopausal women through eNOS phosphorylation [23]. Moreover, fruit vinegar beverages prepared from apple, tomato, cranberry, and blueberry containing more than 10 mg acetic acid/ml showed a concentration-dependent enzyme inhibition in angiotensin converting enzyme assay in vitro [10]. As mentioned earlier, single dose administration of 22 g AV in LDAV group of our study caused significant decrease in DBP and PP compared to control and higher concentrations of AV did not have significant effects. Same result was observed by Johnston et al. in study of apple cider vinegar in reduction of post meal blood sugar in diabetics [25].

The unexpected results achieved in the current work might be attributed to the subjects' differences in term of Mizaj (temperament) in Persian medicine. Temperament refers to a dominant homologous quality (hot, cold, wet,

dry; hot-wet, hot-dry, cold-dry, cold-wet) in composite objects following action and reaction of four elements with specific quality (air: hot and wet; soil: cold and dry; water: cold and wet; fire: hot and dry). According to this theory, medicines have their own temperament and affect our body by their specific qualities. The concept of cold or hot refers to ability of materials to induce excessive heat or cold in the human body. In Persian medicine, physicians cure patients by considering their temperament. For example, hot medicines are prescribed for cold diseases and dry medicines are used for wet diseases to balance the temperament [26-28]. Strength of this theory was evaluated by Zare et al. They studied efficacy of cinnamon with hot and dry quality in patients with diabetes mellitus type II. The authors found that the symptoms were better improved in diabetic patients with wet temperament compared to dry temperament [29].

Based on Persian medicine, vinegar has cold and dry quality and its consumption is contraindicated in individuals with cold temperament [6]. In our work, the subjects' temperament was not studied as a variable. However, it might be possible specific temperament of the LDAV group affects the intervention and resulted in significant decline in DBP and PP. Further studies are needed to identify the impact of temperament on findings of clinical trials. A limitation of our study was the weak statistical power due to the small sample size.

4. Conclusion

This study showed that AV consumption could decrease DBP and PP in healthy people within short-term. With respect to the safety and the approved potential of natural AV in protection of cardiovascular system, determination of its role at different concentrations in modulation of blood pressure in hypertensive patients based on their temperament is recommended for future studies.

5. Conflict of interest

The authors declare that there is no conflict of interest with respect to the current study.

6. Acknowledgment

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References

1. Salari A, Mahdavi-Roshan M, Hasandokht T, Gholipour M, Soltanipour S, Nagshbandi M, et al. Nutritional intake, depressive symptoms and vitamin D status in hypertensive patients in the north of Iran: A case–control study. Hipertension y Riesgo Vascular. 2017; 34(2): 65-71. https://doi.org/10.1016/j.hipert.2016.11.001

2. Tanaka H, Watanabe K, Ma M, Hirayama M, Kobayashi T, Oyama H, et al. The effects of γ-aminobutyric acid, vinegar, and dried bonito on blood pressure in normotensive and mildly or moderately hypertensive volunteers. Journal of Clinical Biochemistry and Nutrition. 2009; 45(1): 93-100. https://doi.org/10.3164/jcbn.09-04

3. Parvinroo S. Nutritional and nonnutritional factors with positive and negative effects on the eye health based on iranian traditional medicine. Journal of Aging Research & Clinical Practice. 2017; 7: 1-2. https://doi.org/10.14283/jarcp.2018.1

4. Kordafshari G, Kenari HM, Esfahani MM, Ardakani MR, Keshavarz M, Nazem E, et al. Nutritional aspects to prevent heart diseases in traditional Persian medicine. Journal of Evidence-based Complementary & Alternative Medicine. 2015; 20(1): 57-64. https://doi.org/10.1177/2156587214553939

5. Heydari M, Dalfardi B, Golzari SE, Habibi H, Zarshenas MM. The medieval origins of the concept of hypertension. Heart Views: the Official Journal of the Gulf Heart Association. 2014; 15(3): 96. https://doi.org/10.4103/1995-705X.144807

6. Aghili Khorasani M. Makhzan al-Advie. Iran University of Medical Science. Research Institute for Islamic and Complementary Medicine. Theran. 2008: 396

7. Tonekaboni MM. Tohfat al-Momenin. Moasese Nashre Shahr. Tehran. 2008: 182

8. Sugiyama S, Fushimi T, Kishi M, Irie S, Tsuji S, Hosokawa N, et al. Bioavailability of acetate from two vinegar supplements: capsule and drink. Journal of Nutritional Science and Vitaminology. 2010; 56(4): 266-269. https://doi.org/10.3177/jnsv.56.266

9. Ali Z, Wang Z, Amir RM, Younas S, Wali A, Adowa N, et al. Potential uses of vinegar as a medicine and related in vivo mechanisms. International Journal for Vitamin and Nutrition Research. 2016; 86(3-4): 127-151. https://doi.org/10.1024/0300-9831/a000440

10. Nandasiri R, Rupasinghe HV. Inhibition of low density lipoprotein oxidation and angiotensin converting enzyme in vitro by functional fruit vinegar beverages. Journal of Food Processing & Beverages. 2013; 1(1): 4.

11. Kondo S, Tayama K, Tsukamoto Y, Ikeda K, Yamori Y. Antihypertensive effects of acetic acid and vinegar on spontaneously hypertensive rats. Bioscience, Biotechnology, and Biochemistry. 2001; 65(12): 2690-2694. https://doi.org/10.1271/bbb.65.2690

12. Sugiyama A, Saitoh M, Takahara A, Satoh Y, Hashimoto K. Acute cardiovascular effects of a new beverage made of wine vinegar and grape juice, assessed using an in vivo rat. Nutrition Research. 2003; 23(9): 1291-1296. https://doi.org/10.1016/S0271-5317(03)00116-7

13. Nishikawa Y, Takata Y, Nagai Y, Mori T, Kawada T. Antihypertensive effect of Kurosu extract, a traditional vinegar produced from unpolished rice, in the SHR rats. Journal of the Japanese Society for Food Science and Technology. 2001; 48(1): 73-75. https://doi.org/10.3136/nskkk.48.73

14. Gheflati A, Bashiri R, Ghadiri-Anari A, Reza JZ, Kord MT, Nadjarzadeh A. The effect of apple vinegar consumption on glycemic indices, blood pressure, oxidative stress, and homocysteine in patients with type 2 diabetes and dyslipidemia: A randomized controlled clinical trial. Clinical Nutrition ESPEN. 2019; 33: 132-138. https://doi.org/10.1016/j.clnesp.2019.06.006

15. Kajimoto O. Effect of a drink containing vinegar on blood pressure in mildly and moderately hypertensive subjects. Kenko Eiyo Shokuhin Kenkyu (J Nutr Food). 2001;4(4):47-60.

16. Kajimoto O. Hypotensive effects of drinks containing vinegar on high normal blood pressure and mild hypertensive subjects. Kenko Eiyo Shokuhin Kenkyu (Journal of Nutritional Food). 2003; 6(1): 51-68.

17. Saduo T, Arita J, Miyamoto S, Iwasaki H, Nishimura A, Kajimoto Y, et al. Antihypertensive effect and safety of a drink containing tomato vinegar in case of long-term intake for subjects with high-normal blood pressure or mild hypertension. Japanese Pharmacology and Therapeutics. 2006; 34: 723-735.

18. Ostman E, Granfeldt Y, Persson L, Bjorck I. Vinegar supplementation lowers glucose and insulin responses and increases satiety after a bread meal in healthy subjects. European Journal of Clinical Nutrition. 2005; 59(9): 983-988. https://doi.org/10.1038/sj.ejcn.1602197

19. Lalande S, Johnson BD. Diastolic dysfunction: a link between hypertension and heart failure. Drugs of Today. 2008; 44(7): 503-513. https://doi.org/10.1358/dot.2008.44.7.1221662

20. Lawes CM, Bennett DA, Feigin VL, Rodgers A. Blood pressure and stroke: an overview of published reviews. Stroke. 2004; 35(3): 776-785. https://doi.org/10.1161/01.STR.0000116869.64771.5A

21. Papadopoulos DP, Papademetriou V. Aggressive blood pressure control and stroke prevention: role of calcium channel blockers. Journal of Hypertension. 2008; 26(5): 844-852. https://doi.org/10.1097/HJH.0b013e3282f4d1d5

22. Fushimi T, Suruga K, Oshima Y, Fukiharu M, Tsukamoto Y, Goda T. Dietary acetic acid reduces serum cholesterol and triacylglycerols in

rats fed a cholesterol-rich diet. British Journal of Nutrition. 2006; 95(5): 916-924. https://doi.org/10.1079/BJN20061740

23. Sakakibara S, Murakami R, Takahashi M, Fushimi T, Murohara T, Kishi M, et al. Vinegar intake enhances flow-mediated vasodilatation via upregulation of endothelial nitric oxide synthase activity. Bioscience, Biotechnology, and Biochemistry. 2010; 74(5): 1055-1061. https://doi.org/10.1271/bbb.90953

24. Brighenti F, Castellani G, Benini L, Casiraghi MC, Leopardi E, Crovetti R, et al. Effect of neutralized and native vinegar on blood glucose and acetate responses to a mixed meal in healthy subjects. European Journal of Clinical Nutrition. 1995; 49(4): 242-247.

25. Johnston CS, Steplewska I, Long CA, Harris LN, Ryals RH. Examination of the antiglycemic properties of vinegar in healthy adults. Annals of Nutrition and Metabolism. 2010; 56(1): 74-79. https://doi.org/10.1159/000272133

26. Miraj S, Alesaeidi S, Kiani S. A systematic review of the relationship between dystempra-ment (sue Mizaj) and treatments and management of diseases (Ilaj and Eslah-e-Mizaj). Electronic Physician. 2016; 8(12): 3378. http://dx.doi.org/10.19082/3378

27.Avicenna, A. Ghanoon dar Teb (Canon). First edition, Volume 1. Sorush Press. Tehran. 2010: 271-278.

28. Kopaei R, Khajegir A, Kiani S. The association between dystemprement and prevention of diseases:a systematic review. Journal of Clinical and Diagnostic Research. 2016; 10(9): 1–6. https://doi.org/10.7860/JCDR/2016/19023.8511

29. Zare R, Shams M, Heydari M, Najarzadeh A, Zarshenas M. Analysis of the efficacy of cinnamon for patients with diabetes mellitus type II based on traditional Persian medicine syndrome differentiation: a randomized controlled trial. Shiraz E-Medical Journal. 2020; 21(7): 1-8. https://doi.org/10.5812/semj.95609