Journal of
Pediatrics and Child Nutrition

Research Article

Effect of Sour Orange (*Citrus Aurantium*) Peels on Cardiometabolic Risk Factors and Markers of Endothelial Function in Overweight and Obese Adolescents: A Triple-Masked Randomized Controlled Trial

Mahin Hashemipour[1], Mehrnaz Moeini[2], Alireza Ghannadi[3] and Roya Kelishadi[4]*

[1]Professor, Department of Pediatric Endocrinology, Isfahan University of Medical Sciences, Isfahan, Iran
[2]Resident, Faculty of Medicine, Department of Pediatrics, Isfahan University of Medical Sciences, Isfahan, Iran
[3]Professor, Department of Pharmacognosy, Isfahan University of Medical Sciences, Isfahan, Iran
[4]Professor, Department of Pediatrics, Isfahan University of Medical Sciences, Isfahan, Iran

***Corresponding Author:** Dr. Roya Kelishadi, Professor of Pediatrics, Child Growth and Development Research Center, Research Institute for Primordial Prevention of Non-communicable Disease, Isfahan University of Medical Sciences, Isfahan, Iran; E-mails: kelishadi@med.mui.ac.ir

Published: December 15, 2015

Abstract:

Background: The role of dietary intervention with fruits containing vitamin C and flavonoid on controlling the consequences of childhood obesity remains to be determined. Sour orange (*Citrus aurantium*) contains flavonoid, pectin and vitamin C. We investigated the effects of sour orange peel and its external membranes on cardiometabolic risk factors and markers of endothelial function in overweight and obese adolescents.

Methods: This triple-masked, randomized controlled trial was conducted for one month in 60 overweight/obese adolescents. Eligible participants were randomly assigned into two groups of equal number receiving daily oral capsules containing sour orange powder or placebo. Fasting blood glucose, lipid profile, systolic and diastolic blood pressure, as well as markers of endothelial function (ICAM-1 and VCAM-1) were compared between two groups before and after the trial.

Results: Of total 60 participants, 27 and 29 patients in the sour orange group and placebo group completed the study, respectively. The baseline characteristics were not significantly different between groups. The intake of sour orange peels and its external membranes had no considerable effect on cardiometabolic risk factors and markers of endothelial function. In the sour orange group, slight reduction was documented in systolic and diastolic blood pressures as well as anthropometric measures after treatment. Comparison of the percent change of variables between groups showed significant difference for systolic and diastolic blood pressures.

Conclusion: Our study showed that consumption of sour orange peels had some slight effects on some cardiometabolic risk factors in overweight and obese adolescents. Extensive lifestyle change should be underscored for weight management of adolescents.

Keywords: Adolescents; Cardiometabolic Risk Factors; Endothelial Function; Obesity; Sour Orange

Introduction:

Childhood obesity is becoming a worldwide problem and it is no more limited to high-income countries. The increasing incidence of childhood obesity in developing countries is going to become an emerging public health problem in the near future [1]. Obesity and overweight, especially among children, are major health concerns in the societies that raised awareness to the potential adverse consequences associated with being overweight. Accumulating evidences suggest that the complications of obesity in adults begin in early childhood. The prevalence of overweight has been significantly increased among children in recent years worldwide. In the united states, 31% of children aged 6-19 were reported overweight or at risk for overweight [2].

According to recent studies, the highest prevalence of childhood overweight was found in Eastern Europe and the Middle East [1].

In Iran, the prevalence of overweight and obesity in children aged 6-18 years was reported as 10.1% and 4.79% based on national cut-off points [3].

Moreover, the results of a meta-regression analysis showed that the escalating trend of excess weight among Iranian young children is alarming and should be considered by providers of interventional preventive programs at national and regional levels [4].

Childhood obesity plays an important role as predisposing factor for most non-communicable diseases. Pediatric Obesity has been shown to be associated with increased prevalence of type 2 diabetes mellitus, hypertension, cardiovascular disease, the metabolic syndrome and dyslipidemia [5,6]. Obesity has also been shown to induce endothelial dysfunction and initiation of atherosclerosis [7]. One the earliest detectable cellular response in the formation of lesions of atherosclerosis is leukocyte adherence to the endothelium at particular anatomic sites in the artery wall. Members of the immunoglobulin superfamily of endothelial adhesion molecules, including ICAM-1 and VCAM-1, mediate firm adhesion and are indicators in case of endothelial damages. Circulating forms of VCAM-1and ICAM-1 have been detected in plasma and are elevated during inflammatory conditions in which detailed pathology studies have documented increased expression of cellular adhesion molecules on endothelial cells and other tissue types [8].

An increasing body of evidences suggest that increase in oxidative factors accounts for a significant proportion of such complications [9]. Therefore, implementation of treatment and prevention programs before adulthood will be more effective [10].

Dietary intervention could play an important role in the control of obesity and its consequences such as dyslipidemia and blood sugar levels [11]. Epidemiological studies indicate an association between increased intake of dietary antioxidants and reduced risk of some diseases, including cardiovascular diseases, cancers and inflammatory disorders [12,13].

In addition, endothelial dysfunction could be reversed by the use of superoxide scavenging agents, such as vitamin C and flavonoids [14].

In many studies, the effects of flavonoid-rich foods on the markers of cardiovascular disease risk has been observed [15-18].

Flavonoids, according to their structure, are reducing agents and can serve as efficient chelators of transition metals involved in cellular oxidation reactions The association between flavonoids, including citrus flavonoids, and metabolic disorders and atherosclerosis has been linked to their antioxidant properties and to a reduction in oxidative stress [19,20].

An inverse relationship between flavonoid consumption and heart disease risk factors including lower blood pressure, improved weight management, and improved dyslipidemia has been determined [11,15].

There is a paucity of information regarding the role of dietary intervention with fruits containing ample amounts of vitamin C and flavonoid on the control of serum lipids and other risk factors in childhood.

Citrus species fruits are considered to contain flavonoid, pectin and vitamin C [21]. It is suggested that drinking citrus juices for few weeks would improve the blood lipid profile, reduces oxidative stress, prevents atherogenic modifications of LDL cholesterol and platelet aggregation and improves HDL-cholesterol concentrations [11,17].

Sour orange is a citrus species Persian fruit, which is used popularly among Iranians as natural additive to several foods and salads. This study aims to investigate the effects of the peels and external membranes of sour orange (*Citrus aurantium*) on cardiometabolic risk factors and markers of endothelial function in overweight and obese adolescents.

Methods:

This triple-masked, randomized controlled trial was conducted in Isfahan/Iran, among 60 overweight/obese adolescents aged 10-18 years. They were randomly selected from clinics of Child Growth and Development Research Center, affiliated to Isfahan University of Medical Sciences, Isfahan, Iran.

Weight, height, as well as waist and neck circumferences were measured according to standard protocols using calibrated instruments. Body mass index (BMI) was calculated by dividing weight in kilograms by the height in meters squared (kg/m^2). According to the revised growth charts of the Centers for Disease Control and Prevention (CDC) in 2000, the 85^{th} to 95^{th} BMI percentiles were considered as overweight and obese, respectively [22].

Those individuals with underlying chronic diseases or on medication or special diet were not recruited. In addition to anthropometric measurements, fasting blood glucose (FBG), lipid profile including total cholesterol, low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), and triglycerides (TG) were determined. Systolic and diastolic blood pressures (SBP and DBP) were also assessed. Cell adhesion molecule–1 (VCAM-1) and intercellular adhesion molecule–1 (ICAM-1) were measured, as markers of endothelial function.
Eligible participants were randomly assigned into two groups of equal number receiving daily oral capsules containing powdered peel of sour orange or placebo.

Using random numbers table, we performed randomization. The table was based on the record numbers of participants. Participants, practitioner and the investigators were kept masked about the grouping. Before treatment initiation, written informed consent that was approved by the Vice chancellery for research of Isfahan University of Medical Sciences was obtained from the parent or legal custodian. The university Research Ethics committee approved the study. This trial was approved and registered in the Iranian Registry of Clinical Trials, which is a Primary Registry in the World Health Organization Registry Network (IRCT-code: 201311231434N11).

The patients in first group received capsules containing powdered peels and external membranes of sour orange for a period of one month. Other patients in the second group received placebo for similar period of time. The study medications were prepared in capsule form in Pharmacognosy department of Isfahan University of Medical Sciences. Well-dried peels and external membranes of sour orange (*Citrus aurantium*) were used to prepare powder. There were bought from Isfahan and Sari markets (these cities are located in center and north of Iran, respectively) and identified in the Isfahan Pharmacognosy department. For placebo receiving group, corn- starch powder was prepared [23]. The powders were filled in capsules, which were same in color and shape and size. Secret codes were defined for each group and then the medications were packed and delivered to the center without any label to prevent study pediatrician, nurses, patients and staff from knowing which medication was received. Only some staffs of the Pharmacy laboratory were aware about the content of capsules; they were not included in the research team. All laboratory tests and physical examinations were repeated after the trial.

Statistical analysis: We used intention-to-treat analysis. Data were analyzed using paired t-test, independent t-test, Chi-square tests, and analysis of covariance (ANCOVA). We reported all values as means ± SE. P_{time}, P_{group} and $P_{time * group}$ were calculated for all variables. Percent change of variables was calculated, for instance for BMI,it was calculated as: $BMI_{after\ treatment}$-$BMI_{baseline}$/$BMI_{baseline}$. SPSS for Windows software (version 20.0, SPSS Inc., Chicago, IL) was used for statistical analysis. The statistical significance level was set as $P<0.05$.

Results:

Of total 60 enrolled patients, 4 subjects were lost to follow up: 1 patient refused to continue, 1 due to moving to another city, and 2 patients did not return for follow-up. There was no statistically significant difference in the number of withdrawals between three groups (P = 0.09). No patient was excluded due to meeting the exclusion criteria.

Finally, 27 patients (mean ± SD of age = 12.2 ± 9.2; 8 boys and 19 girls) in the sour orange group and 29 (mean ± SD of age = 13.2 ± 9.2; 10 males and 19 females) in the control group completed the study period. Comparison of age and sex showed no statistically significant difference between two groups (P = 0.45 for age and P = 0.65 for sex). In addition, no significant difference existed between height, weight, BMI, neck and waist circumferences in two groups at the beginning of the study (Table 1).

Variables	Groups Sour Orange (n = 27)	Placebo (n = 29)	P value
Weight (kg)	48.31±11.08	53.37±13.16	0.12
Body Mass Index (kg/m^2)	23.46±3.18	24.72±3.67	0.17
Waist Circumference (cm)	76.98±9.78	76.90±9.12	0.97
Neck Circumference (cm)	31.91±2.42	31.53±2.25	0.54

Values are mean±SE

Table 1: Anthropometric Measures of Study Participants in the Sour Orange and Placebo Groups

Before the trial, no significant difference existed between SBP, TG, LDL-C, HDL-C, I-CAM and V-CAM between the two groups studied (P>0.05).

Using ANCOVA, all mentioned parameters were again compared between two groups after the trial. At this time, none of the assessed parameters had significant difference between two groups, other than SBP that was decreased after treatment in sour orange group compared to the placebo group (Table2).

Table 2. Variables Values Among Sour Orange and Placebo Groups at Baseline and After One Month of Study

	Groups							
	Sour Orange (n = 27)	Placebo (n = 29)	$P_{overall}$[a]	P_{time}[b]	P_{group}[c]	$P_{time \times group}$[d]	$P_{time \times age}$[e]	$P_{time \times sex}$[f]
Length								
Before	142.64±9.22	146.09±12.16	0.239	0.108	0.955	0.986	0.902	0.781
After	143.40±9.19	146.85±12.09	0.238					
$P_{before,after}$[g]	<0.001	<0.001						
Weight								
Before	48.31±11.08	53.37±13.16	0.127	0.887	0.427	0.116	0.483	0.633
After	47.67±10.90	53.15±12.94	0.094					
$P_{before,after}$[g]	0.004	0.260						
BMI								
Before	23.46±3.18	24.72±3.67	0.178	0.245	0.250	0.204	0.834	0.630
After	22.90±3.07	24.36±3.53	0.106					
$P_{before,after}$[g]	<0.001	<0.001						
Waist								
Before	76.98±9.78	76.90±9.12	0.973	0.103	0.602	0.999	0.517	0.712
After	75.57±9.68	75.60±9.10	0.991					
$P_{before,after}$[g]	0.001	0.012						
Neck								
Before	31.91±2.42	31.53±2.25	0.545	0.045	0.173	0.686	0.137	0.454
After	31.47±2.51	31.07±2.26	0.532					
$P_{before,after}$[g]	0.001	0.001						
BPS								
Before	107.22±9.84	98.90±8.49	0.001	0.255	<0.001	0.079	0.023	0.330
After	103.63±8.27	97.41±6.76	0.003					
$P_{before,after}$[g]	0.017	0.081						
BPD								
Before	70.00±7.34	66.90±8.06	0.139	0.184	0.128	0.020	0.160	0.780
After	68.33±6.65	67.41±7.75	0.637					
$P_{before,after}$[g]	0.095	0.264						
FBS								
Before	87.93±10.04	86.31±6.94	0.484	0.783	0.608	0.318	0.505	0.082
After	86.70±6.95	87.03±6.20	0.851					
$P_{before,after}$[g]	0.450	0.496						
Cholesterol								
Before	175.26±22.05	180.14±38.04	0.557	0.830	0.583	0.980	0.622	0.947
After	172.22±21.88	176.66±33.72	0.565					
$P_{before,after}$[g]	0.327	0.396						
TG								
Before	128.93±57.37	142.76±90.55	0.495	0.938	0.533	0.792	0.110	0.066
After	109.07±41.42	116.07±68.49	0.649					
$P_{before,after}$[g]	0.052	0.013						
HDL								
Before	49.89±14.11	54.62±11.59	0.175	0.951	0.113	0.891	0.451	0.583
After	52.15±13.06	56.86±10.85	0.147					
$P_{before,after}$[g]	0.226	0.085						
LDL								
Before	99.56±27.20	97.26±31.38	0.775	0.720	0.477	0.411	0.682	0.955
After	102.00±25.13	95.00±27.13	0.330					
$P_{before,after}$[g]	0.572	0.412						
ICAM								
Before	6678.52±1439.12	6997.93±1487.78	0.428	0.373	0.325	0.342	0.224	0.587
After	6526.58±1506.98	6832.52±2459.56	0.601					
$P_{before,after}$[g]	0.580	0.617						
VCAM								
Before	18584.36±3434.75	19497.79±3083.30	0.308	0.769	0.254	0.395	0.813	0.892
After	18838.83±4099.92	19237.80±2794.17	0.691					
$P_{before,after}$[g]	0.551	0.568						

All values are mean±SE

[a] *P value present a comparison baseline and end point values between two groups (computed by T-test)*

[b] *P value demonstrate the effect of time (computed by analysis of the covariance)*

[c] *P value demonstrate the effect of grouping (computed by analysis of the covariance)*

[d] *P value demonstrate the time × group interaction (computed by analysis of the covariance)*

[e] *P value demonstrate the time × age interaction (computed by analysis of the covariance)*

[f] *P value demonstrate the time × sex interaction (computed by analysis of the covariance)*

[g] *P values present comparison baseline and end point values within each group (computed by paired sample t test)*

Table 2: Variables Values among Sour Orange and Placebo Groups at Baseline and after One Month of Study

Percent change of variables was compared between two groups. No significant difference was found between the two groups studied (Table 3). The only significant differences were documented for percent changes of SBP and DBP.

Variables	Groups Sour Orange (n = 27)	Placebo (n = 29)	P value
Weight (%)	-1.30±0.20	-0.37±0.19	0.08
BMI (%)	-2.34±0.45	-1.41±0.74	0.1
Waist (%)	-1.80±0.32	-1.65±0.25	0.84
Neck (%)	-1.40±0.88	-1.46±0.12	0.91
SBP (%)	-3.05±0.36	-1.28±0.28	0.02
DBP (%)	-2.10±0.38	0.90±0.08	0.03
FBG (%)	-0.68±0.97	1.09±0.49	0.39
Cholesterol (%)	-1.33±0.23	-1.01±0.12	0.9
TG (%)	-5.78±0.46	-8.16±0.04	0.82
HDL (%)	6.56±0.71	5.46±0.96	0.82
LDL (%)	-6.49±0.80	-0.89±0.96	0.22
ICAM (%)	-5.10±0.21	-1.30±0.27	0.47
VCAM (%)	-4.76±0.10	-0.07±0.01	0.48

Table 3: Percent Change in Variables in the Sour Orange and Placebo Groups at Baseline and After the Trial

Discussion:

Our study showed that the intake of sour orange peels and its external membranes had no considerable effect on cardiometabolic risk factors and markers of endothelial function. Slight reduction was documented in SBP and BMI, as well as in the waist and neck circumferences. However, the mean levels of BMI, waist and neck circumferences had no difference between the participants who had received sour orange compared to placebo.

Citrus flavonoid and Vitamin C which are a main component in citrus species, have marked potentiality in lowering lipid and lipoprotein and can slow the progression of atherosclerosis and endothelial dysfunction [24]. Pectin as a soluble fiber of Citrus fruits has also mild hypocholestrolemic effects [25].

We could not observe any statistical difference in within-group and between-group analysis for HDL, total cholesterol and the LDL. This finding is in line with the results of other studies in which the effect of other types of diets were investigated [26]. Within-group analysis of our study also confirmed the results of a previous study conducted on obese children, aged 7-13 [27]. One possible reason for a lack of change in the blood lipids in both sour orange group and the placebo group is that the adolescents' blood lipids were in the normal range at baseline. These outcomes may have been different if the subjects' lipid homeostasis were disturbed [28].

Further research studies should focus on the link between biochemistry and physiological pattern of the body, especially among pubertal girls.

Obesity, due to molecular and cellular alterations in adipose tissue, is closely associated with various inflammatory processes. As the body fat increases, several pro-inflammatory factors are produced in adipose tissue. Additionally, clinical and experimental data have demonstrated a link between systemic inflammation and endothelial dysfunction. Recent evidences show that disturbed endothelial function may be an early marker of an ongoing atherosclerotic process [29].

As a result, serum markers of inflammation and oxidative stress are associated with the early inflammatory processes of atherosclerosis [30].

Vitamin C inhibits peroxidation of membrane phospholipids and acts as a scavenger of free radicals; moreover it is required for the synthesis of several hormones and neurotransmitters. Supplementation of vitamin C may improve the function of the human immune system and control of inflammation, such as antimicrobial and natural killer cell activities, lymphocyte proliferation, chemotaxis,

and delayed-type hypersensitivity [31]. In is suggested that consumption of antioxidants including fruits rich in vitamin C and flavonoids could result in favorable changes in the process of atherosclerosis [31,32].

It was expected that sour orange which is rich in Vitamin C and flavonoids could affect on endothelial markers such as ICAM and VCAM in this study. But there are several differences between our study and these reported studies. Endothelial markers in our study had no significant difference either in between groups or within group analysis. One of the main reasons for this indifference is related to the duration of the treatment and the needed time to observe the outcomes.

Other markers, which were investigated in other studies, could show the changes in treated patients. Flow mediated dilatation (FMD) of the brachial artery, as a non-invasive endothelial function testing, showed early stages of endothelial dysfunction and was associated with the early inflammatory state in obese children. It is documented that lifestyle change and or consumption of antioxidants might improve FMD in obese adolescents [33-35].

Study limitations and strengths: The study population was relatively small, and the trial duration was short, however some previous trials with herbal medicines had significant results in the same period of time. The other limitation is that we did not measure the body fat percent of participants.

This study has strengths in a number of ways: First, the current trial was triple masked and placebo controlled which causes elimination of selection and observational biases. Secondly, this study was a randomized trial, which results in controlling some effects of potential existing confounding variables.

Conclusion:

We found that consumption of sour orange peel extract and external membranes could have slight effect on some cardiometabolic risk factors in overweight and obese adolescents. Further studies with long follow up are necessary in this regard; extensive changes in the lifestyle habits of obese adolescents should be underscored.

References:

1. Kelishadi R (2007) Childhood overweight, obesity, and the metabolic syndrome in developing countries. Epidemiol Rev 29: 62-76.
2. Hedley AA, Ogden CL, Johnson CL, Carroll MD, Curtin LR, et al. (2004) Prevalence of overweight and obesity among US children, adolescents, and adults,1999-2002. JAMA 291: 2847-2850.
3. Kelishadi R, Ardalan G, Gheiratmand R, Majdzadeh R, Hosseini M, et al. (2008) Thinness, overweight and obesity in a national sample of Iranian children and adolescents: CASPIAN study. Child Care Health Dev 34: 44-54.
4. Kelishadi R, Haghdoost AA, Sadeghirad B, Khajehkazemi R (2014) Trend in the prevalence of obesity and overweight among Iranian children and adolescents: A systematic review and meta-analysis. Nutrition 30: 393-400.
5. Van Gaal LF, Mertens IL, De Block CE (2006) Mechanisms linking obesity with cardiovascular disease. Nature 444: 875-880.
6. Wickelgren I (1998) Obesity: how big a problem? Science 280:1364-1367.
7. Valle Jimenez M, Estepa RM, Camacho RM, Estrada RC, Luna FG, et al. (2007) Endothelial dysfunction is related to insulin resistance and inflammatory biomarker levels in obese prepubertal children. Eur J Endocrinol 156: 497-502.
8. Ballantyne CM, Mainolfi EA, Young JB, Windsor NT, Cocanougher B, et al. (1994) Relationship of increased levels of circulating intercellular adhesion molecule 1 after heart transplantation to rejection: human leukocyte antigen mismatch and survival. J Heart Lung Transplant 13: 597-603.
9. Heitzer T, Just H, Munzel T (1996) Antioxidant vitamin C improves endothelial dysfunction in chronic smokers. Circulation 94: 6-9.
10. Moayeri H, Aghighi Y (2006) Prevalence of hyperlipidemia in a group of obese adolescents in Tehran. IRCMJ 8: 30-125.
11. Kelishadi R, Gidding SS, Hashemi M, Hashemipour M, Zakerameli A, et al. (2011) Acute and long term effects of grape and pomegranate juice consumption on endothelial dysfunction in pediatric metabolic syndrome. J Res Med Sci 16: 245-253.

12. Bernabe J, Mulero J, Cerda B, Garcıa-Viguera C, Moreno DA, et al. (2013) Effects of a citrus based juice on biomarkers of oxidative stress in metabolic syndrome patients. Journal of functional foods 5: 1031-1038.
13. Kushi LH, Folsom AR, Prineas RJ, Mink PJ, Wu Y, et al. (1996) Dietary antioxidant vitamins and death from coronary heart disease in postmenopausal women. N Engl J Med 334: 1156-1162.
14. Ting HH, Timimi FK, Haley EA, Roddy MA, Ganz P, et al. (1997) Vitamin C improves endothelium-dependent vasodilation in forearm resistance vessels of humans with hypercholesterolemia. Circulation 95: 2617-2622.
15. Bazzano LA (2006) The high cost of not consuming fruits and vegetables. J Am Diet Assoc 106: 1364-1368.
16. Hooper L, Kroon PA, Rimm EB, Cohn JS, Harvey I, et al. (2008) Flavonoids, flavonoid-rich foods, and cardiovascular risk: a meta-analysis of randomized controlled trials. Am J Clin Nutr 88: 38-50.
17. Tohill BC, Seymour J, Serdula M, Kettel-Khan L, Rolls BJ (2004) What epidemiologic studies tell us about the relationship between fruit and vegetable consumption and body weight. Nutr Rev 62: 365-374.
18. Kurowska EM, Spence JD, Jordan J, Wetmore S, Freeman DJ, et al. (2000) HDL-cholesterol-raising effect of orange juice in subjects with hypercholesterolemia. American Journal of Clinical Nutrition 72: 1095-1100.
19. Huxley RR, Neil HA (2003) The relation between dietary flavonol intake and coronary heart disease mortality: a meta-analysis of prospective cohort studies. Eur J Clin Nutr 57: 904-908.
20. Aherne SA, O'Brien NM (2000) Mechanism of protection by the flavonoids, quercetin and rutin, against tert-butylhydroperoxide- and menadione-induced DNA single strand breaks in Caco-2 cells. Free Radic Biol Med 29: 507-514.
21. Mulvihill EE, Allister EM, Sutherland BG, Telford DE, Sawyez CG, et al. (2009) Naringenin prevents dyslipidemia, apolipoprotein B overproduction, and hyperinsulinemia in LDL receptor-null mice with diet-induced insulin resistance. Diabetes 58: 2198-2210.
22. Chen YT, Zheng RL, Jia ZJ, Ju Y (1990) Flavonoids as superoxide scavengers and antioxidants. Free Radic Biol Med 9: 19-21.
23. Sabzghabaee AM, Khayam I, Kelishadi R, Ghannadi A, Soltani R, et al. (2013) Effect of Zizyphus jujube fruits on dyslipidemia in obese adolescents: a triple-masked randomized, controlled clinical trial. Med Arch 67: 156-159.
24. Rouhani MH, Kelishadi R, Hashemipour M, Esmaillzadeh A, Azadbakht L (2013) The Effect of an Energy Restricted Low Glycemic Index Diet on Blood Lipids, Apolipoproteins and Lipoprotein (a) Among Adolescent Girls with Excess Weight: a Randomized Clinical Trial. Lipids 48: 1197-1205.
25. Iannuzzi A, Licenziati MR, Vacca M, De Marco D, Cinquegrana G, et al. (2009) Comparison of two diets of varying glycemic index on carotid subclinical atherosclerosis in obese children. Heart Vessel 24: 419-424.
26. Levitan EB, Cook NR, Stampfer MJ, Ridker PM, Rexrode KM, et al. (2008) Dietary glycemic index, dietary glycemic load, blood lipids, and C-reactive protein. Metabolism 57: 437-443.
27. Wang Z, Nakayama T (2010) Inflammation, a link between obesity and cardiovascular disease. Mediators Inflamm 2010:1-17.
28. Kelishadi R, Sharifi M, Khosravi A, Adeli K (2007) Relationship between C-reactive protein and atherosclerotic risk factors and oxidative stress markers among young persons 10–18 years old. Clin Chem 53: 456-464.
29. Shaik-Dasthagirisaheb YB, Varvara G, Murmura G, Saggini A, Caraffa A, et al. (2013) Role of vitamins D, E and C in immunity and inflammation. J Biol Regul Homeost Agents 27: 291-295.
30. Hajjar DP, Gotto AM Jr (2013) Biological relevance of inflammation and oxidative stress in the pathogenesis of arterial diseases. Am J Pathol 182: 1474-1481.
31. Jain AK, Mehra NK, Swarnakar NK (2015) Role of Antioxidants for the Treatment of Cardiovascular Diseases: Challenges and Opportunities. Curr Pharm Des 21: 4441-4455.

32. Cha J, Niedzwiecki A, Rath M (2015) Hypoascorbemia induces atherosclerosis and vascular deposition of lipoprotein (a) in transgenic mice. Am J Cardiovasc Dis 5: 53-62.
33. Engler MM, Engler MB, Malloy MJ, Chiu EY, Schloetter MC, et al. (2003) Antioxidant vitamins C and E improve endothelial function in children with hyperlipidemia: endothelial assessment of risk from lipids in youth (EARLY) trial. Circulation 108: 1059-1063.
34. Kelishadi R, Hashemi M, Mohammadifard N, Asgary S, Khavarian N (2008) Association of changes in oxidative and proinflammatory states with changes in vascular function after a lifestyle modification trial among obese children. Clin Chem 54: 147-153.
35. Hashemi M, Khosravi E, Ghannadi A, Hashemipour M, Kelishadi R (2015) Effect of the peels of two Citrus fruits on endothelium function in adolescents with excess weight: A triple-masked randomized trial. J Res Med Sci 20: 721-726.