

The anti-atherosclerotic effects of tomatoes

Hidekatsu Yanai, Hiroki Adachi, Akiko Kawaguchi, Mariko Hakoshima, Yoko Waragai, Tadanao Harigae, Yoshinori Masui, Koki Kakuta, Hidetaka Hamasaki, Hisayuki Katsuyama, Akahito Sako

Department of Internal Medicine, National Center for Global Health and Medicine Kohnodai Hospital, Chiba, Japan

Corresponding author: Hidekatsu Yanai, MD, PhD, FACP, Department of Internal Medicine, National Center for Global Health and Medicine Kohnodai Hospital, 1-7-1 Kohnodai, Ichikawa, Chiba 272-8516, Japan

Submission date: March 23rd, 2017, **Acceptance Date:** June 27th, 2017, **Publication Date:** June 30th, 2017

Citation: Yanai H, Adachi H, Kawaguchi A, Hakoshima M, Waragai Y, Harigae T, Masui Y., The anti-atherosclerotic effects of tomatoes. *Functional Foods in Health and Disease* 2017; 7(6); 411-428

ABSTRACT

Tomatoes are rich in lycopene, which causes the red coloring of tomatoes. Several reports have suggested lycopene plays a role in the prevention of cardiovascular diseases. In this study, we systematically reviewed the interventional studies using tomatoes or tomato products to understand the anti-atherosclerotic effects of the tomato as a functional food. We found that a significant number of interventional studies reported the anti-atherosclerotic effects of tomatoes, including anti-obesity effects, hypotensive effects, improvement of lipid/glucose metabolism and endothelial function, anti-oxidative and anti-inflammatory effect, and anti-platelet effect; however, the anti-platelet effect was disagreed upon by some studies. Furthermore, we discovered cooking methods significantly affect anti-atherosclerotic effects of tomatoes.

Keywords: anti-oxidative effect, atherosclerosis, body weight, tomatoes, serum lipids

INTRODUCTION

Tomatoes are rich in lycopene, beta-carotene, folate, potassium, vitamin C and E, and flavonoids [1]. Lycopene is a non-provitamin. A carotenoid is responsible for the red color of tomatoes [2]. Several reports have suggested lycopene plays a role in the prevention of cardiovascular diseases (CVD), based upon epidemiological studies that demonstrate a dose-response relationship between lycopene and CVD [3]. In the cross-sectional study between tomato-based food product intake and coronary biomarkers in the Women's Health Study with 27,261 female participants ≥ 45 years and were free of CVD and cancer, women consuming ≥ 10 compared with < 1.5 servings/week of tomato-based food products had significant improvements in total cholesterol (TC) (5.38 vs 5.51 mmol/L; $P = 0.029$), TC/high-density lipoprotein cholesterol (HDL-C) ratio (4.08 vs 4.22; $P = 0.046$), and hemoglobin A1c (HbA1c) (5.02 vs. 5.13%; $P < 0.001$) in multivariable models [4].

In human macrophages, lycopene reduced intracellular TC dose-dependently. This kind of effect was associated with a decrease in cholesterol synthesis through a reduction of activity and expression of 3-hydroxy-3-methylglutaryl coenzyme A reductase, a modulation of low-density lipoprotein (LDL) receptor and acyl-coenzyme A: cholesterol acyltransferase activity [5]. An increase in cholesterol efflux through an enhancement of ATP-binding cassette transporter A1 (ABCA1) and caveolin-1 expression was also observed [5]. Moreover, tomato products have been reported to attenuate the susceptibility of LDL to oxidative modification and inflammatory nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) signaling and to the improvement of endothelial function [6, 7]. The Caco-2 cells were pretreated with lycopene at different concentrations for 24 h and then incubated with radioactive micellar cholesterol for 2 h [8]. Lycopene dose-dependently inhibited cholesterol absorption and reduced expression of Niemann-Pick C1-like 1 (NPC1L1) protein and NPC1L1 mRNA.

In this study, we systematically reviewed the interventional studies using tomatoes or tomato products, to understand anti-atherosclerotic effects of tomato as a functional food. Furthermore, we will discuss methods of cooking tomatoes to increase efficacy to improve atherosclerosis.

The Interventional Trials Investigating Anti-atherosclerotic Effects of Tomatoes or Tomato Products

We looked for interventional trials investigating the anti-atherosclerotic effects of tomatoes or tomato products with PubMed until March 2017 (Table 1). We searched for these trials by using the combination of "tomato" with the following words "plasma glucose, cholesterol, LDL-C, HDL-C, triglyceride (TG), blood pressure (BP), body weight, obesity, atherosclerosis, HbA1c, diabetes, insulin resistance, hypertension, CVD, inflammation, cytokine, anti-platelet and anti-oxidative," and discovered 28 articles.

Table 1. Clinical studies that investigated anti-atherosclerotic effects of tomato and tomato products in humans			
Authors	Study design	Subjects	Results/Conclusions
Anti-obesity effet			
Hirose A, et al. [9]	An open-label, single-arm study. The participants refrained from foods and drinks rich in tomato and tomato-based products for 2 weeks prior to the study and during the 8 weeks of tomato juice consumption. After the run-in period, the women were asked to consume 200 ml of unsalted tomato juice, twice daily for 8 weeks. Measurements were performed at 4 and 8 weeks after study commencement	95 women (40-60 years) who had at least one menopausal symptom	Resting energy expenditures increased (1980±368 kcal/day, 2108±440 kcal/day, 2149±470 kcal/day; P = 0.0030), serum TG decreased in the subgroup of women (n=22) who had high TG (150 mg/dL or higher) at baseline (237.8±88.9 mg/dl, 166.7±86.1 mg/dl, 170.9±109.7 mg/dl; P=0.0002).
Li YF, et al. [10]	The subjects continued with their normal diet and exercise schedule, but were given 280 ml of tomato juice (containing 32.5 mg of lycopene) daily for 2 months	30 young females (20- to 30 years) with BMI ≥ 20 kg/m ²	Tomato juice supplementation significantly reduced body weight, body fat, waist circumference, BMI, and serum TC, monocyte chemoattractant protein-1, and thiobarbituric reactive substances, while significantly increasing serum adiponectin, TG, and lycopene. These effects are unrelated to body fat changes.
Vinha AF, et al. [11]	During 4 weeks, daily, participants ingested a raw ripe tomato (~90g) before lunch. Their anthropometric and biochemical parameters were measured repeatedly during the follow-up time	35 young women (age, 19.6±1.3 years)	Significant reductions were observed on body weight (-1.09±0.12 kg), % fat (-1.54±0.52%), fasting blood glucose (-5.29±0.80 mg/dl), TG (-8.31 ±1.34 mg/dl), TC (-10.17 ±1.21 mg/dl), and uric acid (-0.16±0.04 mg/dl).
Anti-hypertensive effect			
Shidfar F, et al. [12]	Study participants received 200 g raw tomato daily for 8 weeks. Serum glucose, apoB and apoA-I and homocysteine were measured at the beginning and end of 8 weeks.	32 type 2 diabetic patients	There were significant decrease in systolic and diastolic BP and also a significant increase in apoA-I at the end of study compared with initial values (P = 0.0001, P = 0.0001 and P = 0.013, respectively). 200 g raw tomato per day had a favored effect on BP and apoA-I so it might be beneficial for reducing cardiovascular risk associated with type 2 diabetes.
Paran E, et al. [13]	2 double blind cross-over treatment periods of 6 weeks each, with standardized tomato extract or identical placebo. Plasma concentrations of lycopene, nitrite and nitrate were measured and correlated with BP changes was studied	54 subjects with moderate hypertension treated with one or two antihypertensive drugs	There was a significant reduction of systolic BP after 6 weeks of tomato extract supplementation, from 145.8±8.7 to 132.2±8.6 mmHg (P < 0.001) and 140.4±13.3 to 128.7 ±10.4 mmHg (P < 0.001) in the two groups. There was a decline in diastolic BP from 82.1±7.2 to 77.9±6.8 mmHg (P = 0.001) and from 80.1±7.9 to 74.2±8.5 mmHg (P = 0.001). There was no significant change in systolic and diastolic BP during the placebo period. Serum lycopene level increased from 0.11±0.09 to 0.30±0.13 μmol/l after tomato extract therapy (P < 0.001). There was a significant correlation between systolic BP and lycopene levels (r = -0.49, P < 0.001).

Engelhard YN, et al. [14]	A single-blind, placebo-controlled trial. Subjects entered a 4-week placebo period, then an 8-week treatment period with tomato extract, and a 4-week control period with placebo	31 subject with grade-1 hypertension who required no antihypertensive or lipid-lowering drug therapy	Systolic BP decreased from 144±1.1 (mean±SE) to 134±2 mmHg (P < .001), and diastolic BP decreased from 87.4±1.2 to 83.4±1.2 mmHg (P < .05). No changes in BP were demonstrated during placebo periods. Thiobarbituric acid-reactive substances, a lipid peroxidation products marker, decreased from 4.58±0.27 to 3.81±0.32 nmol/mg (P < 0.05). No significant changes were found in lipid parameters.
Improvement of lipid and glucose metabolism			
Bohn T, et al. [15]	A single arm intervention study. Healthy men and women consumed a soy germ-fortified juice daily (300 ml supplying 66 mg isoflavones and 22 mg lycopene) for 8 weeks	18 healthy men and women	Juice consumption significantly improved resistance of LDL+VLDL-C to copper-mediated oxidation (P = 0.039), HDL-C (47.3±15.8 to 51.7±14.8 mg/dl, P < 0.001), and TC:HDL-C ratio (4.25±1.59 to 3.63±1.16, P < 0.001) at 8 weeks.
Silaste ML, et al. [16]	The diet intervention included a baseline period, a 3-week low tomato diet (no tomato products allowed) and a 3-week high tomato diet (400 ml tomato juice and 30 mg tomato ketchup daily)	21 healthy study subjects	TC was reduced by 5.9% (P = 0.002) and LDL-C by 12.9% (P = 0.0002) with the high tomato diet compared to the low tomato diet. The changes in TC and LDL-C correlated significantly with the changes in serum lycopene, beta-carotene and gamma-carotene concentrations. The level of LDL to resist formation of oxidized phospholipids increased 13 % (P = 0.02) in response to the high tomato diet.
Madrid AE, et al. [17]	Study participants received a supplement of pure tomato juice during 7 days. At baseline, at the end of the supplementation period and eight days after the end of the supplementation, a blood sample was drawn	17 healthy volunteers	Lycopene level increased early and significantly in comparison with basal levels (48%; P < 0.05). Total antioxidant capacity, catalase and superoxide dismutase did not change significantly. HDL-C increased significantly in 5.6±4.3 mg/dl (P < 0.002) on the second sampling period, improving TC/HDL-C. It returned to baseline in the third period.
Agarwal S, et al. [18]	Dietary lycopene was provided using tomato juice, spaghetti sauce, and tomato oleoresin for a period of 1 week each. Blood samples were collected at the end of each treatment	19 healthy human subjects	Dietary supplementation of lycopene significantly increased serum lycopene levels by at least twofold. Although there was no change in serum TC, LDL-C, or HDL-C, serum lipid peroxidation and LDL oxidation were significantly decreased.
Collins JK, et al. [19]	Study participants consumed a low lycopene diet with no added lycopene (control) or supplemented with watermelon or tomato juice each containing 20 mg lycopene. Subjects consumed each treatment for 3 weeks in a crossover design	10 healthy men and women	Compared to the control diet, the lycopene-containing foods did not affect plasma lipid concentrations or antioxidant biomarkers.

<p>Cuevas-Ramos D, et al. [20]</p>	<p>A randomized, single-blinded, controlled clinical trial. Study participants completed a 2-week run-in period on an isocaloric diet and then were randomized to receive 300 g of cucumber (control group) or two uncooked Roma tomatoes a day for 4 weeks</p>	<p>50 individuals (women = 41; 82%) with age (42±15.5 years) and BMI (27.6±5.0 kg/m²)</p>	<p>A significant increase in HDL-C was observed in the tomato group (from 36.5±7.5 mg/dl to 41.6±6.9 mg/dl, P < 0.0001 vs. the control group). After stratification by gender, the difference in HDL-C levels was only significant in women. The mean HDL-C increase was 5.0±2.8 mg/dl. A linear regression model that adjusted for parameters that impact HDL-C levels showed an independent association between tomato consumption and the increase in HDL-C (r² = 0.69; P < 0.0001).</p>
<p>Burton-Freeman B, et al. [21]</p>	<p>Study participants consumed high-fat meals to induce postprandial oxidative stress on two separate occasions containing either processed tomato product or non-tomato alternative. Blood samples were collected at 0, 30, 60, 90, 120 min, then hourly until 360 min</p>	<p>12 women and 13 men (age, 27±8 years; BMI, 22±2 kg/m²)</p>	<p>Both meals induced increases in plasma glucose, insulin, and lipid concentrations (P < 0.05). A trend for higher TG at >240 min was observed after the tomato meal (P = 0.006). Tomato significantly attenuated high-fat meal-induced LDL oxidation (P < 0.05) and rise in interleukin-6 (p < 0.0001).</p>
<p>Lazarus SA, et al. [22]</p>	<p>A double-blind, parallel-group clinical trial in which participants were assigned to consume 250 ml of clarified tomato juice (n = 10; 7 men and 3 women) or placebo tomato-flavored beverage (n = 10; 7 men and 3 women) daily for 3 weeks</p>	<p>Patients with type 2 diabetes (n = 18) or impaired glucose tolerance (n = 2). 14 men and 6 women aged 43 to 82 years with BMI (mean±SD, 30.5±4.9 kg/m²)</p>	<p>No significant differences were observed in HbA1c following supplementation with tomato juice (7.1±1.2% vs 6.9±1.0%; P = 0.55) or placebo beverage (6.7±1.0% vs 6.6±1.0%; P = 0.68). Platelet aggregation decreased following supplementation with tomato juice as compared with the placebo group.</p>
<p>Anti-oxidative effect</p>			
<p>Bub A, et al. [23]</p>	<p>Randomly assigned to control (mineral water) or intervention group (tomato juice). Subjects of the tomato juice group consumed daily 330 ml tomato juice for 8 weeks</p>	<p>50 elderly subjects</p>	<p>Tomato juice consumption reduced LDL-oxidation and improved antioxidant status in R-allele carriers (paraoxonase1-192 polymorphism), but not in the QQ genotype group.</p>
<p>Upritchard JE, et al. [24]</p>	<p>Randomized to receive tomato juice (500 ml/day), vitamin E (800 U/day), vitamin C (500 mg/day), or placebo treatment for 4 weeks</p>	<p>57 patients with well-controlled type 2 diabetes aged <75 years</p>	<p>Plasma lycopene levels increased nearly 3-fold (P = 0.001), and the lag time in isolated LDL oxidation by copper ions increased by 42% (P = 0.001) in patients during supplementation with tomato juice, which was almost as effectively as supplementation with a high dose of vitamin E.</p>

García-Alonso FJ, et al. [25]	A 2-week intervention trial involving the daily intake of 500 ml of n-3 PUFA-enriched juice (n = 11) or plain tomato juice (n = 7). Each serving of enriched juice provided 250 mg of EPA plus DHA. Both juices provided natural antioxidant compounds such as phenolics (181 mg) and lycopene (26.5 mg)	18 healthy women	Intervention with the enriched juice had no effect on serum lipid profile. The serum antioxidant status improved following juice intake, as revealed by an increase in total antioxidant capacity and a slight decrease in lipid peroxidation. Serum homocysteine decreased following n-3 PUFA-enriched juice consumption. A decrease in vascular adhesion molecule 1 was also noted after intake of either plain or enriched tomato juice, whereas intercellular adhesion molecule 1 only decreased following intake of the enriched juice.
Pourahmadi Z, et al. [26]	Randomly allocated to the intervention group consuming 330 ml/day of tomato juice (n = 40) or control consuming water (n = 35), for a 20-day period.	75 overweight or obese female students	Lycopene consumption had no effect on total antioxidant capacity and antioxidant enzyme activity (superoxide dismutase, glutathione peroxidase, and catalase).
Ghavipour M, et al. [27]	Randomly received tomato juice (n = 32, 330 ml/day) or water (n = 28) for 20 days	64 overweight or obese (BMI ≥ 25 kg/m ²) female students	Plasma total antioxidant capacity and erythrocyte antioxidant enzymes increased and serum malondialdehyde decreased in the intervention group compared with baseline and with the control group (P < 0.05). In the intervention group, similar results were found in overweight, but not in obese, subjects.
Lee CY, et al. [28]	Placebo (rice and olive oil) or tomato (tomato sauce, rice and olive oil) meals were provided to the volunteers. Blood and urine samples were taken before consumption of meal (0 h) and 2, 4, 6, 24 and 48 h after meal	10 Healthy male subjects	Consumption of tomato sauce increased plasma lycopene level by 5-22%, with a maximum level at 24 h (P < 0.01) after the meal. Plasma F(2)-isoprostanes, hydroxyeicosatetraenoic acid products, allantoin and urinary 8-hydroxy-2'-deoxyguanosine did not change after either meal, but urinary F(2)-isoprostanes (P < 0.05) significantly decreased at 48 h compared to 0 h after the tomato sauce meal.
Deplanque X, et al. [29]	In a randomized, double-blind, parallel-groups, placebo-controlled study, study participants were randomly assigned to a daily dose of carotenoid-rich tomato extract or placebo during 2 weeks. Oxidized LDL, glucose, insulin, and TG were measured for 8 h after ingestion of a high-fat meal before and at the end of intervention	146 healthy normal weight individuals	Plasma lycopene, phytofluene, and phytoene were increased throughout the study period in the carotenoid-rich tomato extract group compared to placebo. Carotenoid-rich tomato extract ingestion significantly improved changes in oxidized LDL response to high-fat meal compared to placebo after 2 weeks (P < 0.0001). Changes observed in glucose, insulin, and TG were not statistically significant after 2 weeks of supplementation.
Bub A, et al. [30]	In this randomized cross-over study, study participants on a low-carotenoid diet received 330 ml/day tomato juice (37.0 mg lycopene, 1.6 mg beta-carotene) or carrot juice (27.1 mg beta-carotene, 13.1 mg alpha-carotene) for 2 weeks	22 healthy, non-smoking men	Tomato juice consumption had no significant effects on paraoxonase 1 activity. However, tomato juice consumption reduced (P < 0.05) plasma malondialdehyde in QR/RR (paraoxonase 1-192 genotypes) as compared to QQ subjects.

Anti-platelet effect			
O'Kennedy N, et al. [31]	A 7-h time-course study was carried out in subjects to determine the ex vivo efficacy of a supplement drink containing tomato extract and the onset and duration of antiplatelet effects	23 cannulated human subjects	A significant inhibition of baseline platelet function, from $2.9 \pm 1.4\%$ (optimal ADP concentrations; $P = 0.03$) to $20.0 \pm 4.9\%$ (suboptimal ADP concentrations; $P < 0.001$), 3 h after supplementation with a dose of tomato extract equivalent to 6 tomatoes was observed. The observed effects persisted for >12 h. Coagulation variables were not affected.
O'Kennedy N, et al. [32]	A randomized, double-blinded, placebo-controlled crossover study. Changes from baseline hemostatic function were measured 3 h after consumption of tomato extract-enriched or control supplements	90 healthy human subjects selected for normal platelet function	Significant reductions in ex vivo platelet aggregation induced by ADP and collagen were observed 3 h after supplementation with doses of tomato extract equivalent to 6 and 2 tomatoes. No significant effects were observed for control supplements. A dose response to tomato extract was found at low levels of platelet stimulation. Inhibition of platelet function was greatest in a subgroup with the highest plasma homocysteine ($P < 0.05$) and C-reactive protein concentrations ($P < 0.001$).
Anti-inflammatory effect			
Thies F, et al. [33]	After a 4-week run-in period with a low-tomato diet, study participants were randomly assigned into a control diet group (low in tomato-based foods), a high-tomato-based diet group, or a control diet supplemented with lycopene capsules group (10 mg/day) for 12 weeks. Blood samples were collected at baseline, at 6 weeks, and after the intervention	225 volunteers (94 men and 131 women) aged 40-65 years	None of Inflammatory markers, markers of insulin resistance and sensitivity, and lipid concentrations and arterial stiffness changed significantly after the dietary intervention. These data indicate that a relatively high daily consumption of tomato-based products (equivalent to 32-50 mg lycopene/day) or lycopene supplements (10 mg/day) is ineffective at reducing conventional CVD risk markers in moderately overweight, healthy, middle-aged individuals.
Ghavi pour M, et al. [34]	Randomly allocated to an intervention group (n=53) or a control group (n=53) consuming 330 ml/day of tomato juice or water, respectively, for 20 days	106 overweight or obese female students	Serum interleukin-8 and tumor necrosis factor- α decreased significantly in the intervention group compared with the control group and with baseline. This effect was confined to subjects with overweight. Among obese subjects, serum interleukin-6 was decreased in the intervention group compared with the control group, with no differences in interleukin-8 and tumor necrosis factor- α observed.

Effect on endothelial function			
Xaplanteris P, et al. [35]	A randomized, single-blind, crossover design. The study consisted of a supplementation arm (70 g tomato paste containing 33.3 mg of lycopene) and a control arm, during which no tomato paste was added to their regular diet	19 volunteers (age, 39±13 years; 8 men/11 women)	Tomato supplementation led to an overall flow-mediated dilatation increase compared with the control period (P = 0.047). At day 1, flow-mediated dilatation was not significantly increased (P = 0.329). By day 15, tomato supplementation resulted in an increase in flow-mediated dilatation by 3.3±1.4%, whereas at the control arm, flow-mediated dilatation declined by -0.5±0.6% (P = 0.03). Total oxidative status decreased at the end of the supplementation period compared with baseline values (P = 0.038).
Stangl V, et al. [36]	Randomised study participants to consume a buttered roll with and without tomato purée (70 g) in a cross-over design. Endothelial-dependent flow-mediated dilation and endothelial-independent nitro-mediated dilation of the brachial artery were assessed. Acute (24 h) and long-term (7 days) effects were examined after daily consumption of the tested meal	19 healthy non-smoking postmenopausal women	Plasma lycopene levels increased from 0.30 to 0.42 and to 0.74 µm after 24 h and 7 days, respectively, with tomato purée consumption. These data indicated an effective absorption of the tomato product. However, both acute and long-term tomato purée consumption had no effects on endothelium-dependent or -independent dilation of the brachial artery.

BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HDL-C, high-density lipoprotein-cholesterol; HbA1c, hemoglobin A1c; LDL, low-density lipoprotein; PUFA, polyunsaturated fatty acids; TC, total cholesterol; TG, triglyceride; VLDL-C, very low-density lipoprotein-cholesterol

Anti-obesity effect

In an open-label, single-arm study, the women were asked to consume 200 ml of unsalted tomato juice, twice daily for 8 weeks. Resting energy expenditures significantly increased from 1980±368 kcal/day to 2108±440 kcal/day after 4 weeks and 2149±470 kcal/day after 8 weeks, which could contribute to anti-obesity effect [9]. Two-month tomato juice supplementation significantly reduced body weight, body fat, waist circumference, and BMI in young females with BMI over 20 kg/m² [10]. During 4 weeks, young women ingested a raw ripe tomato (90 g/day) before lunch. Significant reductions were observed on body weight (-1.09 ± 0.12 kg) and % fat (-1.54 ± 0.52%) [11].

Anti-hypertensive effect

Thirty-two type 2 diabetic patients received 200 g raw tomato daily for 8 weeks. There was a significant reduction in systolic and diastolic BP at the end of study compared with the baseline [12]. In 2 double blind cross-over treatment periods of 6 weeks with standardized tomato extract or placebo, 54 subjects with moderate hypertension treated with one or two antihypertensive drugs were enrolled. There was a significant reduction in systolic BP after 6 weeks of tomato extract supplementation, from 145.8 ± 8.7 to 132.2 ± 8.6 mmHg and 140.4 ± 13.3 to 128.7 ± 10.4 mmHg in the two groups [13]. There was a decline in diastolic BP from 82.1 ± 7.2 to 77.9 ± 6.8 mmHg and from 80.1 ± 7.9 to 74.2 ± 8.5 mmHg. There was no significant change in systolic and diastolic BP during the placebo period. There was a significant correlation between systolic BP and lycopene levels. In a single-blind, placebo-controlled trial, 31 subject with grade-1 hypertension who required no anti-hypertensive or lipid-lowering drug therapy entered a 4-week placebo period, then an 8-week treatment period with tomato extract, and a 4-week control period with placebo [14]. Systolic BP significantly decreased from 144 ± 1.1 (mean \pm SE) to 134 ± 2 mmHg, and diastolic BP decreased from 87.4 ± 1.2 to 83.4 ± 1.2 mmHg. No changes in BP were demonstrated during placebo periods.

Improvement of lipid and glucose metabolism

Ingestion of tomato and tomato-based products decreased serum TG in women with high TG [9]. Two-month tomato juice supplementation significantly reduced serum TC, while significantly increasing serum TG, in addition to reduction of body weight, body fat, waist circumference, and BMI. These effects are unrelated to changes in body fat [10]. Four-week ingestion of a raw ripe tomato before lunch lead to reduction in fasting blood glucose (-5.29 ± 0.80 mg/dl), TG (-8.31 ± 1.34 mg/dl), and TC (-10.17 ± 1.21 mg/dl) [11]. Daily 200 g raw tomato for 8 weeks induced a significant increase in apoA-I, which is the main apolipoprotein of HDL ($P = 0.013$) [12].

Reduction of TC [10, 11, 16], LDL-C [16], TC/HDL-C [15, 17], TG [9], and plasma glucose [11] by ingestion of tomato have been reported. However, increase in TG by tomato ingestion was reported in two trials [10, 21]. Elevation of HDL-C [15, 17, 20] by tomato ingestion were observed in three trials. A significant influence of tomato ingestion on serum lipids were denied by three trials [14, 18, 19].

In a double-blind, parallel-group clinical trial, patients with type 2 diabetes or impaired glucose tolerance were assigned to consume 250 ml of tomato juice or placebo tomato-flavored beverage daily for 3 weeks [22]. No significant differences were observed in HbA1c following

supplementation with tomato juice ($7.1 \pm 1.2\%$ vs $6.9 \pm 1.0\%$; $P = 0.55$) or placebo beverage ($6.7 \pm 1.0\%$ vs $6.6 \pm 1.0\%$; $P = 0.68$).

Anti-oxidative effect

A lipid peroxidation products maker was significantly decreased by an 8-week treatment with tomato extract [14]. A soy germ-fortified juice (22 mg lycopene) consumption for 8 weeks improved resistance of LDL and very low-density lipoprotein (VLDL) to copper-mediated oxidation [15]. A 3-week high tomato diet increased the LDL level to resist formation of oxidized phospholipids [16]. A single administration of processed tomato product significantly attenuated high-fat meal-induced LDL oxidation [21]. Other seven trials suggested that tomato or tomato product ingestion increased antioxidant capacity and the resistance of LDL to oxidation [23-25, 27-30, 36].

However, in the study by Madrid AE, a 7-day supplement of pure tomato juice did not change total anti-oxidant capacity, catalase and superoxide dismutase [17]. A 3-week consumption of tomato juice containing 20 mg lycopene and 330 ml/day of tomato juice for 20 days also did not affect anti-oxidant biomarkers [19, 26].

Anti-platelet effect

Platelet aggregation decreased following supplementation with tomato juice for 3 weeks as compared with the placebo group [22]. A 7-h time-course study was carried out in subjects to determine the ex vivo efficacy of a supplement drink containing tomato extract and the onset and duration of anti-platelet effects [31]. A significant inhibition of baseline platelet function 3 h after supplementation with a dose of tomato extract equivalent to 6 tomatoes was observed. The observed effects persisted for >12 h. Coagulation variables were not affected. In a randomized, double-blinded, placebo-controlled crossover study, significant reductions in ex vivo platelet aggregation induced by ADP and collagen were observed 3 h after supplementation with doses of tomato extract equivalent to 6 and 2 tomatoes [32]. No significant effects were observed for control supplements. A dose response to tomato extract was found at low levels of platelet stimulation.

Anti-inflammatory effect

Reduction of monocyte chemoattractant protein-1 [10], vascular adhesion molecule 1 [25], interleukin-6, interleukin-8, and tumor necrosis factor- α [34] by ingestion of tomato juice were observed. However, in another study, a tomato-based diet failed to reduce inflammatory markers

[33].

Effect on endothelial function

A randomized, single-blind, crossover study consisted of a supplementation arm (70 g tomato paste containing 33.3 mg of lycopene) and a control arm [35]. Tomato supplementation led to an increase in flow-mediated dilatation compared with the control period. At day 1, flow-mediated dilatation was not significantly increased. By day 15, tomato supplementation resulted in an increase in flow-mediated dilatation, while at the control arm flow-mediated dilatation declined. In a randomized cross-over study, participants were asked to consume a buttered roll with and without tomato purée (70 g) [36]. Plasma lycopene levels increased after 24 h and 7 days, respectively, with tomato purée consumption. However, both acute and long-term tomato purée consumption had no effects on endothelium-dependent or -independent dilation of the brachial artery.

The limitation of present study

We have to mention the limitation of our study. We searched the interventional trials investigating anti-atherosclerotic effects of tomato or tomato products using only Pubmed. Admittedly, we should have used not less than three search engines.

Influences of cooking methods of tomatoes on anti-atherosclerotic effects

An assessment of the consumption of tomato products, plasma lycopene concentration, and their interrelationship in a nationally representative sample of elderly British people was performed [37]. Consumption of tomatoes made a significant contribution to plasma lycopene concentration. Age, plasma cholesterol concentration, and smoking habit determined plasma lycopene concentration. Ganji V, et al. investigate the relation between serum lycopene concentrations and sex, age, geographical location, race-ethnicity, education, alcohol, smoking, BMI, BP, serum TC and TG, and intakes of fat, tomatoes and tomato-based products in 3,413 individuals aged 17-90 years by using data from the Third National Health and Nutrition Examination Survey, 1988-1994 [38]. Sex, age, geographical region, socioeconomic status, serum TC, smoking, and intakes of fat, tomatoes, pizza, and pasta were significant determinants of serum lycopene concentrations in the United States.

How should we cook tomatoes to improve anti-atherosclerotic effects? Tangerine tomatoes (*Solanum lycopersicum*) are rich in tetra-cis-lycopene, a result from natural variation in carotenoid isomerase. A marked 8.5-fold increase in lycopene bioavailability with tangerine tomato juice

compared to red tomato juice was observed [39]. In a split plot design, 17 men and women consumed tomatoes which had received minimal additional heating and 16 others consumed extensively additionally heated tomatoes (1 h at 100°C) [40]. These tomatoes were not mildly or severely homogenized. Homogenization significantly increased plasma lycopene [40]. Additional heating tended to increase plasma lycopene [40]. Similar effects to those for lycopene were discovered for beta-carotene.

In a comparative study the availability of a low oral lycopene dosage of 5 mg/day from different food matrices was assessed [41]. Twenty-two female adults were randomized in three groups and were advised to minimize their carotenoid intake for two weeks. After supplementation with tomato juice, the plasma lycopene increased significantly, while remaining unchanged during intake of tomatoes, thereby suggesting that lycopene from tomato juice (processed tomatoes) was better absorbed from the intestine than lycopene from raw tomatoes [41]. Thirty-six healthy subjects consumed a lycopene-free diet for 2 weeks and were then assigned to one of three ($n = 12$) intervention groups consuming daily, single servings of sauce (21 mg lycopene per (1/2) cup), soup (12 mg lycopene per 1 cup), or juice (17 mg lycopene per 8 oz) for 4 weeks [42]. Following intervention, plasma lycopene concentrations increased significantly for the sauce, soup, and juice compared with baseline by 192% ($P < 0.0001$), 122% ($P < 0.0001$) and 92% ($P < 0.0001$), respectively. Ingestion of tomato paste was found to yield 2.5-fold higher total lycopene peak concentration ($P < 0.005$) and 3.8-fold higher area under the curve responses ($P < 0.001$) than ingestion of fresh tomatoes, indicating that the bioavailability of lycopene is greater from tomato paste than from fresh tomatoes in humans [43]. Stahl W, et al. studied the uptake of lycopene from processed (boiled with 1% corn oil for 1 h) and unprocessed tomato juice in humans [44]. Lycopene concentrations in human serum increased only when processed tomato juice was consumed. To evaluate the effect of adding oil to tomato juice (not treated with heat) on the bioavailability of plasma carotenoids and postprandial lipid response, a randomized, controlled, crossover feeding trial was performed [45]. Eleven healthy volunteers were assigned to receive a single ingestion of 750g of tomato juice containing 10% of refined olive oil and 750g of tomato juice without oil on two different days. All lycopene isomers increased significantly in subjects consuming tomato juice with oil, and LDL-C and TC decreased significantly 6h after the consumption of tomato juice with oil, which correlated significantly with an increase of trans-lycopene and 5-cis-lycopene, respectively. To test the postprandial effects of a single dose of raw tomatoes, tomato sauce, and tomato sauce with refined olive oil on cardiovascular disease risk factors, Valderas-Martinez P, et al. performed an open, prospective, randomized, cross-over,

controlled feeding trial in 40 healthy subjects who randomly received: raw tomatoes, tomato sauce, tomato sauce with refined olive oil and sugar water on a single occasion on four different days [46]. A single tomato intake in any form decreased plasma TC, TG, and plasma inflammatory biomarkers, and increased plasma HDL-C compared to the control intervention. The changes of plasma interleukin-6 and vascular cell adhesion molecule-1, and lymphocyte function-associated antigen-1 from T-lymphocytes and CD36 from monocytes were significantly greater after tomato sauce with refined olive oil than after raw tomatoes and tomato sauce interventions, concluding that tomato intake has beneficial effects on cardiovascular risk factors, especially cooked and enriched with oil. Burton-Freeman B, et al. examined clinical trials comparing the efficacy of lycopene supplements with tomato products on CVD risk factors including oxidative stress, inflammation, endothelial function, BP, and lipid metabolism [47]. With the exception of BP management where lycopene supplementation was favored, tomato intake provided more favorable results on cardiovascular risk endpoints than lycopene supplementation did.

CONCLUSION

A significant number of interventional studies reported the anti-atherosclerotic effects of tomatoes, including anti-obesity effect, hypotensive effect, improvement of lipid/glucose metabolism and endothelial function, and anti-oxidative and anti-inflammatory effects, in addition to anti-platelet effect. We also discovered cooking methods significantly affect anti-atherosclerotic effects of tomatoes. However, since a tomato-based diet did not show efficacy in some studies, we should make a clear cut difference between tomatoes and tomato-based diet. Thus, we should perform more studies that focus on the active components of tomatoes.

Abbreviations: ATP-binding cassette transporter A1 (ABCA1); body mass index (BMI); blood pressure (BP); cardiovascular disease (CVD); docosahexaenoic acid (DHA); eicosapentaenoic acid (EPA); high-density lipoprotein-cholesterol (HDL-C); hemoglobin A1c (HbA1c); low-density lipoprotein (LDL); Niemann-Pick C1-like 1 (NPC1L1); nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B); polyunsaturated fatty acids (PUFA); total cholesterol (TC); triglyceride (TG); very low-density lipoprotein-cholesterol (VLDL-C)

Competing Interests: The authors have no financial interests or conflicts of interest.

Authors' contribution: All authors contributed to this study.

REFERENCES

1. Willcox JK, Catignani GL, Lazarus S. Tomatoes and cardiovascular health. *Crit Rev Food Sci Nutr.* 2003; 43:1-18.
2. Story EN, Kopec RE, Schwartz SJ, Harris GK. An update on the health effects of tomato lycopene. *Annu Rev Food Sci Technol.* 2010; 1:189-210.
3. Mordente A, Guantario B, Meucci E, Silvestrini A, Lombardi E, Martorana GE, Giardina B, Böhm V. Lycopene and cardiovascular diseases: an update. *Curr Med Chem.* 2011; 18:1146-63.
4. Sesso HD, Wang L, Ridker PM, Buring JE. Tomato-based food products are related to clinically modest improvements in selected coronary biomarkers in women. *J Nutr.* 2012; 142:326-33.
5. Palozza P, Catalano A, Simone RE, Mele MC, Cittadini A. Effect of lycopene and tomato products on cholesterol metabolism. *Ann Nutr Metab.* 2012; 61:126-34.
6. Maruyama C, Imamura K, Oshima S, Suzukawa M, Egami S, Tonomoto M, Baba N, Harada M, Ayaori M, Inakuma T, Ishikawa T. Effects of tomato juice consumption on plasma and lipoprotein carotenoid concentrations and the susceptibility of low density lipoprotein to oxidative modification. *J Nutr Sci Vitaminol (Tokyo).* 2001; 47:213-21.
7. Armoza A, Haim Y, Bashiri A, Wolak T, Paran E. Tomato extract and the carotenoids lycopene and lutein improve endothelial function and attenuate inflammatory NF-κB signaling in endothelial cells. *J Hypertens.* 2013; 31:521-9
8. Zou J, Feng D. Lycopene reduces cholesterol absorption through the downregulation of Niemann-Pick C1-like 1 in Caco-2 cells. *Mol Nutr Food Res.* 2015; 59:2225-30.
9. Hirose A, Terauchi M, Tamura M, Akiyoshi M, Owa Y, Kato K, Kubota T. Tomato juice intake increases resting energy expenditure and improves hypertriglyceridemia in middle-aged women: an open-label, single-arm study. *Nutr J.* 2015; 14:34.
10. Li YF, Chang YY, Huang HC, Wu YC, Yang MD, Chao PM. Tomato juice supplementation in young women reduces inflammatory adipokine levels independently of body fat reduction. *Nutrition.* 2015; 31:691-6.
11. Vinha AF, Barreira SV, Costa AS, Alves RC, Oliveira MB. Pre-meal tomato (*Lycopersicon esculentum*) intake can have anti-obesity effects in young women? *Int J Food Sci Nutr.* 2014; 65:1019-26.
12. Shidfar F, Froghifar N, Vafa M, Rajab A, Hosseini S, Shidfar S, Gohari M. The effects of tomato consumption on serum glucose, apolipoprotein B, apolipoprotein A-I,

- homocysteine and blood pressure in type 2 diabetic patients. *Int J Food Sci Nutr.* 2011; 62:289-94.
13. Paran E, Novack V, Engelhard YN, Hazan-Halevy I. The effects of natural antioxidants from tomato extract in treated but uncontrolled hypertensive patients. *Cardiovasc Drugs Ther.* 2009; 23:145-51.
 14. Engelhard YN, Gazer B, Paran E. Natural antioxidants from tomato extract reduce blood pressure in patients with grade-1 hypertension: a double-blind, placebo-controlled pilot study. *Am Heart J.* 2006; 151:100.
 15. Bohn T, Blackwood M, Francis D, Tian Q, Schwartz SJ, Clinton SK. Bioavailability of phytochemical constituents from a novel soy fortified lycopene rich tomato juice developed for targeted cancer prevention trials. *Nutr Cancer.* 2013; 65:919-29.
 16. Silaste ML, Alfthan G, Aro A, Kesäniemi YA, Hörkkö S. Tomato juice decreases LDL cholesterol levels and increases LDL resistance to oxidation. *Br J Nutr.* 2007; 98:1251-8.
 17. Madrid AE, Vásquez ZD, Leyton AF, Mandiola C, Escobar FJA. Short-term *Lycopersicon esculentum* consumption may increase plasma high density lipoproteins and decrease oxidative stress. *Rev Med Chil.* 2006; 134:855-62.
 18. Agarwal S, Rao AV. Tomato lycopene and low density lipoprotein oxidation: a human dietary intervention study. *Lipids.* 1998; 33:981-4.
 19. Collins JK, Arjmandi BH, Claypool PL, Perkins-Veazie P, Baker RA, Clevidence BA. Lycopene from two food sources does not affect antioxidant or cholesterol status of middle-aged adults. *Nutr J.* 2004;3:15.
 20. Cuevas-Ramos D, Almeda-Valdés P, Chávez-Manzanera E, Meza-Arana CE, Brito-Córdova G, Mehta R, Pérez-Méndez O, Gómez-Pérez FJ. Effect of tomato consumption on high-density lipoprotein cholesterol level: a randomized, single-blinded, controlled clinical trial. *Diabetes Metab Syndr Obes.* 2013; 6:263-73.
 21. Burton-Freeman B, Talbot J, Park E, Krishnankutty S, Edirisinghe I. Protective activity of processed tomato products on postprandial oxidation and inflammation: a clinical trial in healthy weight men and women. *Mol Nutr Food Res.* 2012; 56:622-31.
 22. Lazarus SA, Bowen K, Garg ML. Tomato juice and platelet aggregation in type 2 diabetes. *JAMA.* 2004; 292:805-6.
 23. Bub A, Barth S, Watzl B, Briviba K, Herbert BM, Lührmann PM, Neuhäuser-Berthold M, Rechkemmer G. Paraoxonase 1 Q192R (PON1-192) polymorphism is associated with reduced lipid peroxidation in R-allele-carrier but not in QQ homozygous elderly subjects

- on a tomato-rich diet. *Eur J Nutr.* 2002; 41:237-43.
24. Upritchard JE, Sutherland WH, Mann JI. Effect of supplementation with tomato juice, vitamin E, and vitamin C on LDL oxidation and products of inflammatory activity in type 2 diabetes. *Diabetes Care.* 2000; 23:733-8.
25. García-Alonso FJ, Jorge-Vidal V, Ros G, Periago MJ. Effect of consumption of tomato juice enriched with n-3 polyunsaturated fatty acids on the lipid profile, antioxidant biomarker status, and cardiovascular disease risk in healthy women. *Eur J Nutr.* 2012; 51:415-24.
26. Pourahmadi Z, Mahboob S, Saedisomeolia A, Reykandeh MT. The Effect of Tomato Juice Consumption on Antioxidant Status in Overweight and Obese Females. *Women Health.* 2015; 55:795-804.
27. Ghavipour M, Saedisomeolia A, Djalali M, Sotoudeh G, Eshraghyan MR, Moghadam AM, Wood LG. Tomato juice consumption reduces systemic inflammation in overweight and obese females. *Br J Nutr.* 2013; 109:2031-5.
28. Lee CY, Isaac HB, Huang SH, Long LH, Wang H, Gruber J, Ong CN, Kelly RP, Halliwell B. Limited antioxidant effect after consumption of a single dose of tomato sauce by young males, despite a rise in plasma lycopene. *Free Radic Res.* 2009; 43:622-8.
29. Deplanque X, Muscente-Paque D, Chappuis E. Proprietary tomato extract improves metabolic response to high-fat meal in healthy normal weight subjects. *Food Nutr Res.* 2016; 60:32537.
30. Bub A, Barth SW, Watzl B, Briviba K, Rechkemmer G. Paraoxonase 1 Q192R (PON1-192) polymorphism is associated with reduced lipid peroxidation in healthy young men on a low-carotenoid diet supplemented with tomato juice. *Br J Nutr.* 2005; 93:291-7.
31. O'Kennedy N, Crosbie L, van Lieshout M, Broom JI, Webb DJ, Duttaroy AK. Effects of antiplatelet components of tomato extract on platelet function in vitro and ex vivo: a time-course cannulation study in healthy humans. *Am J Clin Nutr.* 2006; 84:570-9.
32. O'Kennedy N, Crosbie L, Whelan S, Luther V, Horgan G, Broom JI, Webb DJ, Duttaroy AK. Effects of tomato extract on platelet function: a double-blinded crossover study in healthy humans. *Am J Clin Nutr.* 2006; 84:561-9.
33. Thies F, Masson LF, Rudd A, Vaughan N, Tsang C, Brittenden J, Simpson WG, Duthie S, Horgan GW, Duthie G. Effect of a tomato-rich diet on markers of cardiovascular disease risk in moderately overweight, disease-free, middle-aged adults: a randomized controlled trial. *Am J Clin Nutr.* 2012; 95:1013-22.

34. Ghavipour M, Sotoudeh G, Ghorbani M. Tomato juice consumption improves blood antioxidative biomarkers in overweight and obese females. *Clin Nutr.* 2015; 34:805-9.
35. Xaplanteris P, Vlachopoulos C, Pietri P, Terentes-Printzios D, Kardara D, Alexopoulos N, Aznaouridis K, Miliou A, Stefanadis C. Tomato paste supplementation improves endothelial dynamics and reduces plasma total oxidative status in healthy subjects. *Nutr Res.* 2012; 32:390-4.
36. Stangl V, Kuhn C, Hentschel S, Jochmann N, Jacob C, Böhm V, Fröhlich K, Müller L, Gericke C, Lorenz M. Lack of effects of tomato products on endothelial function in human subjects: results of a randomised, placebo-controlled cross-over study. *Br J Nutr.* 2011; 105:263-7.
37. Re R, Mishra GD, Thane CW, Bates CJ. Tomato consumption and plasma lycopene concentration in people aged 65 y and over in a British national survey. *Eur J Clin Nutr.* 2003; 57:1545-54.
38. Ganji V, Kafai MR; Third National Health and Nutrition Examination Survey, 1998-1994. Population determinants of serum lycopene concentrations in the United States: data from the Third National Health and Nutrition Examination Survey, 1988-1994. *J Nutr.* 2005; 135:567-72.
39. Cooperstone JL, Ralston RA, Riedl KM, Haufe TC, Schweiggert RM, King SA, Timmers CD, Francis DM, Lesinski GB, Clinton SK, Schwartz SJ. Enhanced bioavailability of lycopene when consumed as cis-isomers from tangerine compared to red tomato juice, a randomized, cross-over clinical trial. *Mol Nutr Food Res.* 2015; 59:658-69.
40. van het Hof KH1, de Boer BC, Tijburg LB, Lucius BR, Zijp I, West CE, Hautvast JG, Weststrate JA. Carotenoid bioavailability in humans from tomatoes processed in different ways determined from the carotenoid response in the triglyceride-rich lipoprotein fraction of plasma after a single consumption and in plasma after four days of consumption. *J Nutr.* 2000; 130:1189-96.
41. Böhm V, Bitsch R. Intestinal absorption of lycopene from different matrices and interactions to other carotenoids, the lipid status, and the antioxidant capacity of human plasma. *Eur J Nutr.* 1999; 38:118-25.
42. Allen CM1, Schwartz SJ, Craft NE, Giovannucci EL, De Groff VL, Clinton SK. Changes in plasma and oral mucosal lycopene isomer concentrations in healthy adults consuming standard servings of processed tomato products. *Nutr Cancer.* 2003; 47:48-56.
43. Gärtner C, Stahl W, Sies H. Lycopene is more bioavailable from tomato paste than from

- fresh tomatoes. *Am J Clin Nutr.* 1997; 66:116-22.
44. Stahl W, Sies H. Uptake of lycopene and its geometrical isomers is greater from heat-processed than from unprocessed tomato juice in humans. *J Nutr.* 1992; 122:2161-6.
45. Arranz S, Martínez-Huélamo M, Vallverdu-Queralt A, Valderas-Martinez P, Illán M, Sacanella E, Escribano E, Estruch R, Lamuela-Raventos RM. Influence of olive oil on carotenoid absorption from tomato juice and effects on postprandial lipemia. *Food Chem.* 2015; 168:203-10.
46. Valderas-Martinez P, Chiva-Blanch G, Casas R, Arranz S, Martínez-Huélamo M, Urpi-Sarda M, Torrado X, Corella D, Lamuela-Raventós RM, Estruch R. Tomato Sauce Enriched with Olive Oil Exerts Greater Effects on Cardiovascular Disease Risk Factors than Raw Tomato and Tomato Sauce: A Randomized Trial. *Nutrients.* 2016; 8:170.
47. Burton-Freeman B, Sesso HD. Whole food versus supplement: comparing the clinical evidence of tomato intake and lycopene supplementation on cardiovascular risk factors. *Adv Nutr.* 2014; 5:457-85.