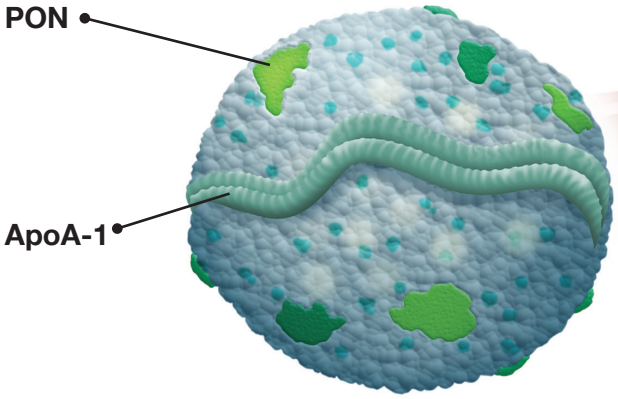
Treating HDL Dysfunction

Bioactives and lifestyle factors can improve HDL function. Here you'll see the mechanisms supported.



Endothelial effects:
- Vasodilation
- Flow-mediated vasodilation
- Reduction of ischemia
- Endothelial nitric oxide production

HDL composition effects:
- HDL-P
- HDL size/maturation
- HDL type
- Activity/expression/modification of:
  - PON
  - apoA-I
  - LCAT
  - CETP
  - SAA

Cholesterol loaded cell effects:
- ↑Increase cholesterol efflux
- ↓Reduce macrophage cytokine secretion
- ↓Reduce LDL oxidation
- ↓Reduce intima-media thickness
- ↓Reduce reactive oxygen species

Liver effects:
Increased expression and activity of cholesterol transporters involved in accepting cholesterol from HDL particles

KEY:

P pomegranate polyphenols	N niacin	Q quercetin
L lycopene	α-T α-tocopherol	M Mediterranean diet
exercise	no smoking	

Other abbreviations:

- **ApoA-I**: apolipoprotein A-I; responsible for cholesterol transport into HDL particle.
- **CETP**: cholesteryl ester transfer protein; serum protein involved in lipid exchange between lipoprotein classes. Inhibiting this protein has been a drug target action for reducing atherosclerosis.
- **LCAT**: lecithin-cholesterol acyltransferase; packs cholesterol into the HDL core.
- **PON**: paraoxonase; protects HDL particle
- **SAA**: Serum amyloid A; an acute-phase inflammatory protein that can displace functional proteins on HDL particles.

Pomegranate Clinical Evidence Related to HDL Function and Cardiovascular Health

Ingredient	Study Design	Main Findings
Pomegranate juice (130 mg/day GAE polyphenols)[1]	Clinical study in men with T2D (n=6); 50 mL/day for 4 wk	• Increased PON1 binding to HDL via reduction in oxidative stress
Pomegranate juice (130 mg/day total polyphenols) or pomegranate polyphenol extract (650 mg/day total polyphenols)[2]	Clinical study in adults with T2D (n=30) ; 50 mL/day juice for 4 wk or 5 mL day extract for 6 wk	• Increased PON1 activity vs. baseline • Increased PON1 protein binding to HDL vs. baseline • Decreased serum oxidative stress vs. baseline
Pomegranate juice*[3]	Clinical study in adults with T2D (n=50); 200 mL/day for 6 wk	• Increased PON activity vs. baseline • Decreased serum MDA vs. baseline • Improved serum fasting glucose, total cholesterol, and LDL cholesterol vs. baseline
Pomegranate juice*[4]	Clinical study in patients with CAS; 10 were supplemented for 1 year, and 5 continued for 3 years	• Increased serum PON1 activity vs. baseline • Reduced intima-media thickness vs. baseline • Reduced LDL oxidation at vs. baseline • Increased serum total antioxidant status vs. baseline
Pomegranate juice (1.5 mM/day total polyphenols)[5]	Clinical study in healthy male volunteers (n=3 or 13); 50 mL/day for 2 wk	• Increased serum PON activity vs. baseline • Reduced HDL oxidation *ex vivo* vs. baseline • Increased plasma total antioxidant status vs. baseline
Pomegranate juice (1.5 mM/day total polyphenols)[6]	Clinical study in healthy men (n=10) and men with T2D (n=10); 50 mL/day for 3 mo	• Increased serum PON1 activity vs. baseline • Reduced serum lipid peroxides vs. baseline • Reduced oxidative stress in macrophages vs. baseline
Pomegranate juice*[7]	RCT in subjects at moderate risk for CHD (n=289); 240 mL/day or placebo for up to 18 mo	• Slowed carotid intima-media thickness progression in subjects with increased oxidative stress
Pomegranate extract (650 mg/day GAE polyphenols)[8]	RCT in hypercholesterolemic adults receiving statin (n=23); 650 mg/day or placebo for 2 mo	• Decreased oxidative stress in monocyte-derived macrophages vs. baseline
Pomegranate extract[9]	RCT in individuals with BMI ≥ 25 (n=48); 1,000 mg/day or placebo for 1 mo	• Decreased inflammatory biomarkers, serum hs-CRP and IL-6 • Decreased lipid peroxidation biomarker, serum MDA • Improved serum fasting glucose, insulin, total cholesterol, HDL cholesterol, and triglycerides
Pomegranate juice*[10]	RCT in patients who had CHD and MI (n=45); 240 mL/day or placebo for 3 mo	• Decreased stress-induced ischemia
Concentrated pomegranate juice (350 mg/day total polyphenols)[11]	Clinical study in patients with T2D and hyperlipidemia (n=22); 40 g/day for 8 wk	• Improved serum lipids (total cholesterol, LDL cholesterol, total cholesterol/HDL cholesterol, LDL cholesterol/HDL cholesterol) vs. baseline
Concentrated pomegranate juice (3.15 mg/day total polyphenols)[12]	Clinical study in adults with T2D (n=40); 50 g/day for 4 wk	• Reduced serum levels of IL-6 vs. baseline • Increased serum total antioxidant capacity vs. baseline

*Amount of total polyphenols was not specified for these studies. Analysis of commercially available pomegranate juice has indicated total polyphenol content ranging from 3.15–437.5 mg/50 mL (/50 g).

BMI= body mass index; **CAS**= carotid artery stenosis; **CHD**= coronary heart disease; **GAE**= gallic acid equivalents; **HDL**= high-density lipoprotein; **hs-CRP**= high-sensitivity C-reactive protein; **IL**= interleukin; **LDL**= low-density lipoprotein; **MDA**= malondialdehyde; **MI**= myocardial ischemia; **mo**= month(s); **PON**= paraoxonase; **RCT**= randomized controlled trial; **T2D**= type 2 diabetes; **wk**= week(s)

Quercetin Clinical and Preclinical Evidence Related to HDL Function and Cardiovascular Health

Ingredient	Study Design	Main Findings
Onion extract[13]	Clinical study in healthy men (n=23); 4.3 g/day containing 51 mg/day quercetin for 1 mo	• Improved postprandial flow-mediated vasodilation vs. baseline
Quercetin[14]	Female C57BL/6 mice; 0.05-2 mg/g diet for 6 wk	• Increased hepatic mRNA and protein levels of PON1 vs. control
Quercetin[15]	LDLR$^{-/-}$ mice fed an atherogenic liquid diet; 0-25 mg/dL quercetin for 8 wk	• Decreased aortic plaques in the ≥ 12.5 mg/dL groups • Increased liver and serum PON1 mRNA expression in the ≥ 12.5 mg/dL groups
Quercetin[16]	*apoE1*$^{-/-}$ mice fed a high-fat diet; 12.5 mg/kg/day or placebo for 8 wk	• Increased cholesterol efflux from macrophages to HDL • Increased cholesterol transport to the liver and bile for excretion
Quercetin[17]	Rats; 10 mg/L or control for 4 wk	• Increased hepatic expression of PON1 • Increased serum and liver PON1 activities • Protected against LDL oxidation
Quercetin[18]	*apoE1*$^{-/-}$ mice fed a high-fat diet; 12.5 mg/kg/day or atorvastatin 2.06 mg/kg/day or control for 12 wk	• Reduced serum levels of oxLDL • Reduced TNF-α and IL-6 levels • Reduced areas of atherosclerotic plaque and increased plaque stability at the aortic root • Increased PPARγ, LXRα, and ABCA1 protein levels in aortas and livers
Quercetin[19]	Rabbits fed high-fat diets; 0.05 mg/kg/day or control for 12 wk (aortic atherosclerosis model) or 4 wk (injured carotid artery model)	• Reduced formation of atherosclerotic plaques in both models
Quercetin[20]	Male Wistar rats; receiving quercetin (dosage n/a) or control	• Increased expression and activity of hepatic cholesterol 7α-hydroxylase • Increased expression and activity of hepatic ABCG1
Quercetin[21,22]	*In vitro* model	• Enhanced cholesterol efflux from RAW264.7 macrophages • Increased ABCA1 mRNA and protein expression in macrophages
Quercetin[23]	*In vitro* model	• Increased cholesterol efflux from foam cells • Activated PPARγ-LXRα pathway to upregulate ABCA1 expression
Quercetin[24]	*In vitro* model	• Induced apoA-I protein and mRNA synthesis in HepG2 (hepatocytes) and Caco-2 (intestinal) cells

ABCA1= ATP-binding cassette transporter A1; **ABCG1**= ATP-binding cassette transporter G1; **apoA-I**= apolipoprotein A-I; **HDL**= high-density lipoprotein; **IL**= interleukin; **LDL**= low-density lipoprotein; **LXR**= liver X receptor; **mo**= month(s); **mRNA**= messenger RNA; **oxLDL**= oxidized LDL; **PON**= paraoxonase; **PPAR**= peroxisome proliferator-activated receptor; **TNF**= tumor necrosis factor; **wk**= week(s)

Lycopene Clinical and Preclinical Evidence Related to HDL Function and Cardiovascular Health

Ingredient	Study Design	Main Findings
Lycopene-rich diet or lycopene supplement[25]	RCT in overweight subjects (n=54); lycopene-rich diet (224-350 mg/wk) or lycopene supplement (70 mg/wk) or control diet for 12 wk	• Increased serum HDL2 and HDL3 • Decreased SAA levels in serum and HDL3 • Increased PON1 activity in serum, HDL2, and HDL3 • Increased LCAT activity in serum and HDL3 • Decreased CETP activity in serum
Tomato[26]	Clinical study in patients with T2D (n=32); 200 g/day tomato for 8 wk	• Increased apoA-I vs. baseline • Decreased systolic and diastolic blood pressure vs. baseline
Lycopene[27]	RCT in statin-treated patients with CVD (n=36) and healthy volunteers (n=36); 7 mg/day or placebo for 2 mo	• Improved endothelium-dependent vasodilatation in patients with CVD
Lycopene and lutein[28]	RCT in subjects with subclinical atherosclerosis (n=144); 20 mg/day lycopene + 20 mg/day lutein for 12 mo	• Decreased carotid artery intima-media thickness vs. baseline
Lycopene[29]	RCT in healthy men (n=126); 6 mg/day or 15 mg/day or placebo for 8 wk	• Increased plasma superoxide dismutase activity • Reduced DNA damage (oxidative stress) in lymphocytes • Increased endothelial function in 15 mg/day group vs. baseline • Decreased hs-CRP, sICAM-1, and sVCAM-1 in 15 mg/day group vs. baseline
Cooked tomato sauce[30]	Pigs fed a hypercholesterolemic diet; 100 g/day containing 21.5 mg/day lycopene or none for 10 days	• Improved HDL function associated with apoA-I and apoJ • Prevented diet-induced impairment of endothelial-dependent coronary vasodilation • Enhanced eNOS transcription and activation and diminished DNA damage in the coronary arteries • Reduced lipid peroxidation
Lycopene[31]	Diabetic rats and control rats; receiving 10 mg/kg/day or none for 1 mo	• Increased PON1 activity
Lycopene[32]	Rabbits fed a high-fat diet; 4-12 mg/kg lycopene or none for 4 and 8 wk	• Reduced serum MDA • Reduced oxLDL • Reduced IL-1 • Increased total antioxidant capacity • Increased nitric oxide • Reduced atherosclerotic plaques in the aorta
Lycopene[33,34]	*In vitro* model	• Increased expression of ABCA1
Lycopene[35]	*In vitro* model	• Reduced proinflammatory cytokine secretion and expression in THP-1 macrophages • Reduced reactive oxygen species production

ABCA1= ATP-binding cassette transporter A1; **apoA-I**= apolipoprotein A-I; **apoJ**= apolipoprotein J; **CETP**= cholesterol ester transfer protein; **CVD**= cardiovascular disease; **DNA**= deoxyribonucleic acid; **eNOS**= endothelial nitric oxide synthase; **HDL**= high-density lipoprotein; **hs-CRP**= high-sensitivity C-reactive protein; **IL**= interleukin; **LCAT**= lecithin cholesterol acyltransferase; **MDA**= malondialdehyde; **mo**= month(s); **oxLDL**= oxidized LDL; **PON**= paraoxonase; **RCT**= randomized controlled trial; **SAA**= serum amyloid A; **sICAM-1**= soluble intercellular adhesion molecule-1; **sVCAM-1**= soluble vascular cell adhesion molecule-1; **T2D**= type 2 diabetes; **wk**= week(s)

α-tocopherol Clinical and Preclinical Evidence Related to HDL Function and Cardiovascular Health

Ingredient	Study Design	Main Findings
α-tocopherol[36]	RCT in individuals with hypercholesterolemia (n=69); 500 IU/day or placebo for 3 mo	• Increased apoA-I levels • Increased apoA-I/apoB ratio
α-tocopherol[37]	RCT in healthy subjects (n=32); 134 mg/day or 268 mg/day or placebo for up to 28 days	• Increased plasma apoA-I concentration in a time- and dose-dependent manner
α-tocopherol[38]	RCT in patients with T2D (n=83); 400 IU/day or placebo for 8 wk	• Increased PON1 activity and total antioxidant status
α-tocopherol[39]	Clinical study in athletes (n=10) in training; 200 mg/day for 1 mo	• Decreased PON1 postexercise; α-tocopherol prevented decreases in PON1 activity postexercise
α-tocopherol[40]	Clinical study in male patients with T2D (n=80); 300 mg/day for 4 wk	• Decreased SAA vs. baseline • Decreased TNF-α and hs-CRP vs. baseline
α-tocopherol[41]	Rabbits fed atherogenic diets; 125 IU/day or 1.25 IU/day (control) for 12 wk	• Reduced total cholesterol levels • Reduced esterified artery cholesterol levels

apoA-I= apolipoprotein A-I; **apoB**= apolipoprotein B; **hs-CRP**= high-sensitivity C-reactive protein; **mo**= month(s); **PON**= paraoxonase; **RCT**= randomized controlled trial; **SAA**= serum amyloid A; **T2D**= type 2 diabetes; **TNF**= tumor necrosis factor; **wk**= week(s)

Niacin Clinical Evidence Related to HDL Function and Cardiovascular Health		
Ingredient	**Study Design**	**Main Findings**
Niacin[42]	RCT in patients with a history of CVD (n=126) receiving atorvastatin 10-80 mg/day; 2 g/day or none for 1 yr	• Increased HDL-C by 39%, HDL-P by 14% and total cholesterol efflux capacity by 16% • Increased large HDL particles • Reduced small HDL particles
Extended-release niacin + laropiprant[43]	Crossover RCT in statin-treated patients (n=27) who had not achieved the LDL-C target; niacin/laropiprant 1 g/20 mg for 4 wk and then 2 g/40 mg for 8 wk or placebo for 8 wk (4 wk wash-out period)	• Significant reduction in total cholesterol, triglycerides, LDL-C, apoB, Lp(a), CETP activity, oxLDL, Lp-PLa2, lysoPC, MCP-1, SAA • No change in HDL antioxidant capacity or PON1 activity • 19.5% increase in cholesterol efflux capacity of HDL
Extended-release niacin[44]	Comparison crossover study in dyslipidemia patients (n=66) with low or normal HDL-C; fenofibrate 160 mg/day for 6 wk or niacin 0.5 g/day for 3 wk and then 1 g/day for 3 wk (4 wk wash-out period)	• Both treatments had a comparable increase in HDL-C and apoA-I, with minor changes in cholesterol efflux capacity
Extended-release niacin[45]	Crossover RCT in patients with metabolic syndrome (n=37); fenofibrate 160 mg/day for 6 wk or niacin 0.5 g/day for 3 wk and then 1 g/day for 3 wk (4 wk wash-out period)	• After either treatment patients had HDL with similar endothelial protective properties as from healthy control subjects • After treatment HDL particles improved endothelial nitric oxide production

apoA-I= apolipoprotein A-I; **apoB**= apolipoprotein B; **CETP**=cholesteryl ester transfer protein; **HDL-C**= HDL-cholesterol; **HDL-P**= HDL particle number; **LDL-C**= LDL-cholesterol; **Lp(a)**= lipoprotein(a); **Lp-PLa2**= lipoprotein phospholipase A2; **lysoPC**= lysophosphatidyl choline; **MCP-1**= macrophage chemoattractant protein; **oxLDL**= oxidized LDL; **PON**= paraoxonase; **RCT**= randomized controlled trial; **SAA**= serum amyloid A

Diet and Lifestyle Clinical Evidence Related to HDL Function and Cardiovascular Health

Diet or Lifestyle	Study Design	Main Findings
Mediterranean diet[46]	RCT of Mediterranean diet enriched with virgin olive oil (n=100) or nuts (n=100) compared to low-fat diet (n=96) in patients with high cardiovascular risk for 1 yr	• Improved HDL cardioprotective functions • Increased PON activity, cholesterol efflux capacity, vasodilation, and improved HDL composition • All diets increased percentage of large HDL particles
Mediterranean dietary components[47]	Secondary analysis of high cardiovascular risk patients (n=296) from PREDIMED clinical trial 1 yr data	• Increasing virgin olive oil (10 g/d) and whole grain (25 g/d) consumption increases cholesterol efflux capacity • Increasing nut (30 g/d), legume (25 g/d), and fish (25 g/d) intake improves PON activity
Fruits and vegetables[48]	RCT in subjects with obesity and T2D; 1 or ≥ 6 portions/day for 8 wk	• ≥ 6 portions/day increased PON1 and LCAT activities in HDL3
Improving dietary quality and increasing physical activity levels[49]	CT in men with obesity and dyslipidemia (n=113); 160 min/wk moderate intensity aerobic activity + moderate caloric restriction (-500 kcal/day) with macronutrient composition of 45-50% carbohydrate, 20-25% protein and 25-30% from fat for 1 yr; compared with control group (n=32)	• Increased cholesterol efflux capacity • Increased apoA-I levels
Smoking cessation[50]	CT in smokers (n=28) in a smoking cessation program using either varenicline or a transdermal nicotine patch for 12 wk	• Improved cholesterol efflux capacity and HDL inflammatory index compared to participants who were unable to quit smoking
Smoking cessation[51]	RCT in smokers (n=923); smoking cessation pharmacotherapies for 1 yr	• Participants who quit smoking (36.2%) had increases in HDL-C, HDL-P, and large HDL • Effects were more pronounced in women
Effect of smoking[52]	Clinical study in young smokers (n=21) and healthy controls (n=20) comparing lipoprotein parameters	• HDL from young smokers (< 10 cigarettes/d x 3 yrs) had lower antioxidant capacity, smaller particle size, and increased triglyceride content
Vigorous prolonged exercise[53]	RCT in 2 cohorts; first group with sedentary adults with prediabetes with BMI 25-35 (n=106) and the second group with similar but nondiabetic adults (n=90); varying levels of exercise for 6 mo	• Vigorous endurance exercise improved cholesterol efflux capacity • Non-ABCA1 cholesterol efflux capacity improved in highest intensity group • An exercise intensity or dosage threshold may need to be exceeded to see significant results • Exercise matures HDL particles (pre-β to α-HDL)
Exercise[54]	RCT of women with obesity (n=32); combined aerobic and resistance exercise (moderate-vigorous intensity, 40-60 min, 4x/wk) or control for 12 wk	• HDL subclasses were restored to "nonobese" state in this population • Decreased PON activity, antithrombotic actions, and distribution of small HDL particles—participants did not lose significant amount of weight • Cholesterol efflux capacity unchanged
Exercise-based cardiac rehabilitation[55]	Retrospective analysis of patients (n=57) with acute coronary syndrome who completed or dropped out (used as control) of an exercise-based program (gymnastics and aerobic exercise) 30 min, 3-5x/wk for 6 mo	• Increased HDL cholesterol efflux capacity in participants who successfully completed the program and stopped smoking • Program increased exercise capacity
Therapeutic lifestyle changes[56]	Prospective pilot study in patients with metabolic syndrome (n=25); 180 min/wk of exercise at 85% maximum heart rate for 12 wk	• Reduced oxidation molecules associated with HDL activity • Increased cholesterol efflux capacity

ABCA1= ATP-binding cassette transporter A1; **apoA-I**= apolipoprotein A-I; **BMI**= body mass index; **CT**= clinical trial; **HDL**= high-density lipoprotein; **LCAT**= lecithin cholesterol acyltransferase; **mo**= month(s); **PON**= paraoxonase; **RCT**= randomized controlled trial; **T2D**= type 2 diabetes; **wk**= week(s); **yr**= year(s)

References

1. Fuhrman B et al. Pomegranate juice polyphenols increase recombinant paraoxonase-1 binding to high-density lipoprotein: studies in vitro and in diabetic patients. *Nutrition.* 2010;26:359-366.
2. Rock W et al. Consumption of wonderful variety pomegranate juice and extract by diabetic patients increases paraoxonase 1 association with high-density lipoprotein and stimulates its catalytic activities. *J Agric Food Chem.* 2008;56:8704-8713.
3. Parsaeyan N et al. Effect of pomegranate juice on paraoxonase enzyme activity in patients with type 2 diabetes. *J Diabetes Metab Disord.* 2012;11:11.
4. Aviram M et al. Pomegranate juice consumption for 3 years by patients with carotid artery stenosis reduces common carotid intima-media thickness, blood pressure and LDL oxidation. *Clin Nutr.* 2004;23:423-433.
5. Aviram M et al. Pomegranate juice consumption reduces oxidative stress, atherogenic modifications to LDL, and platelet aggregation: studies in humans and in atherosclerotic apolipoprotein E-deficient mice. *Am J Clin Nutr.* 2000;71:1062-1076.
6. Rosenblat M et al. Anti-oxidative effects of pomegranate juice (PJ) consumption by diabetic patients on serum and on macrophages. *Atherosclerosis.* 2006;187:363-371.
7. Davidson MH et al. Effects of consumption of pomegranate juice on carotid intima-media thickness in men and women at moderate risk for coronary heart disease. *Am J Cardiol.* 2009;104:936-942.
8. Hamoud S et al. Pomegranate extract (POMx) decreases the atherogenicity of serum and of human monocyte-derived macrophages (HMDM) in simvastatin-treated hypercholesterolemic patients: a double-blinded, placebo-controlled, randomized, prospective pilot study. *Atherosclerosis.* 2014;232:204-210.
9. Hosseini B et al. Effects of pomegranate extract supplementation on inflammation in overweight and obese individuals: A randomized controlled clinical trial. *Complement Ther Clin Pract.* 2016;22:44-50.
10. Sumner MD et al. Effects of pomegranate juice consumption on myocardial perfusion in patients with coronary heart disease. *Am J Cardiol.* 2005;96:810-814.
11. Esmaillzadeh A et al. Cholesterol-lowering effect of concentrated pomegranate juice consumption in type II diabetic patients with hyperlipidemia. *Int J Vitam Nutr Res.* 2006;76:147-151.
12. Shishehbor F et al. Effects of concentrated pomegranate juice on subclinical inflammation and cardiometabolic risk factors for type 2 diabetes: a quasi-experimental study. *Int J Endocrinol Metab.* 2016;14:e33835.
13. Nakayama H et al. Chronic intake of onion extract containing quercetin improved postprandial endothelial dysfunction in healthy men. *J Am Coll Nutr.* 2013;32:160-164.
14. Boesch-Saadatmandi C et al. Effect of quercetin on paraoxonase 1 activity--studies in cultured cells, mice and humans. *J Physiol Pharmacol.* 2010;61:99-105.
15. Leckey LC et al. Quercetin and ethanol attenuate the progression of atherosclerotic plaques with concomitant up regulation of paraoxonase1 (PON1) gene expression and PON1 activity in LDLR-/- mice. *Alcohol Clin Exp Res.* 2010;34:1535-1542.
16. Cui Y et al. Quercetin improves macrophage reverse cholesterol transport in apolipoprotein E-deficient mice fed a high-fat diet. *Lipids Health Dis.* 2017;16:9.
17. Gong M et al. Quercetin up-regulates paraoxonase 1 gene expression with concomitant protection against LDL oxidation. *Biochem Biophys Res Commun.* 2009;379:1001-1004.
18. Jia Q et al. Quercetin protects against atherosclerosis by regulating the expression of PCSK9, CD36, PPARgamma, LXRalpha and ABCA1. *Int J Mol Med.* 2019;44:893-902.
19. Juzwiak S et al. Effect of quercetin on experimental hyperlipidemia and atherosclerosis in rabbits. *Pharmacol Rep.* 2005;57:604-609.
20. Zhang M et al. Quercetin regulates hepatic cholesterol metabolism by promoting cholesterol-to-bile acid conversion and cholesterol efflux in rats. *Nutr Res.* 2016;36:271-279.
21. Chang YC et al. Quercetin enhances ABCA1 expression and cholesterol efflux through a p38-dependent pathway in macrophages. *J Lipid Res.* 2012;53:1840-1850.
22. Lee SM et al. Quercetin up-regulates expressions of peroxisome proliferator-activated receptor gamma, liver X receptor alpha, and ATP binding cassette transporter A1 genes and increases cholesterol efflux in human macrophage cell line. *Nutr Res.* 2013;33:136-143.
23. Sun L et al. Quercetin increases macrophage cholesterol efflux to inhibit foam cell formation through activating PPARgamma-ABCA1 pathway. *Int J Clin Exp Pathol.* 2015;8:10854-10860.
24. Haas MJ et al. Induction of hepatic apolipoprotein A-I gene expression by the isoflavones quercetin and isoquercetrin. *Life Sci.* 2014;110:8-14.
25. McEneny J et al. Lycopene intervention reduces inflammation and improves HDL functionality in moderately overweight middle-aged individuals. *J Nutr Biochem.* 2013;24:163-168.
26. Shidfar F et al. 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;62:289-294.
27. Gajendragadkar PR et al. Effects of oral lycopene supplementation on vascular function in patients with cardiovascular disease and healthy volunteers: a randomised controlled trial. *PLoS One.* 2014;9:e99070.
28. Zou ZY et al. Effects of lutein and lycopene on carotid intima-media thickness in Chinese subjects with subclinical atherosclerosis: a randomised, double-blind, placebo-controlled trial. *Br J Nutr.* 2014;111:474-480.
29. Kim JY et al. Effects of lycopene supplementation on oxidative stress and markers of endothelial function in healthy men. *Atherosclerosis.* 2011;215:189-195.
30. Vilahur G et al. Intake of cooked tomato sauce preserves coronary endothelial function and improves apolipoprotein A-I and apolipoprotein J protein profile in high-density lipoproteins. *Transl Res.* 2015;166:44-56.
31. Yegin SC et al. Effect of lycopene application in rats with experimental diabetes using lipoprotein, paraoxonase and cytokines. *J Membr Biol.* 2013;246:621-626.
32. Hu MY et al. Comparison of lycopene and fluvastatin effects on atherosclerosis induced by a high-fat diet in rabbits. *Nutrition.* 2008;24:1030-1038.
33. Yang CM et al. Lycopene inhibits the proliferation of androgen-dependent human prostate tumor cells through activation of PPARgamma-LXRalpha-ABCA1 pathway. *J Nutr Biochem.* 2012;23:8-17.
34. Yang CM et al. Lycopene and the LXRalpha agonist T0901317 synergistically inhibit the proliferation of androgen-independent prostate cancer cells via the PPARgamma-LXRalpha-ABCA1 pathway. *J Nutr Biochem.* 2012;23:1155-1162.
35. Palozza P et al. Lycopene prevention of oxysterol-induced proinflammatory cytokine cascade in human macrophages: inhibition of NF-kappaB nuclear binding and increase in PPARgamma expression. *J Nutr Biochem.* 2011;22:259-268.
36. Cloarec MJ et al. Alpha-tocopherol: effect on plasma lipoproteins in hypercholesterolemic patients. *Isr J Med Sci.* 1987;23:869-872.
37. Aldred S et al. Alpha tocopherol supplementation elevates plasma apolipoprotein A1 isoforms in normal healthy subjects. *Proteomics.* 2006;6:1695-1703.
38. Rafraf M et al. Vitamin E improves serum paraoxonase-1 activity and some metabolic factors in patients with type 2 diabetes: no effects on nitrite/nitrate levels. J*ournal of the American College of Nutrition.* 2016;35:521-528.
39. Tsakiris S et al. Alpha-tocopherol supplementation prevents the exercise-induced reduction of serum paraoxonase 1/arylesterase activities in healthy individuals. *Eur J Clin Nutr.* 2009;63:215-221.
40. Jamalan M et al. Effect of ascorbic acid and alpha-tocopherol supplementations on serum leptin, tumor necrosis factor alpha, and serum amyloid A levels in individuals with type 2 diabetes mellitus. *Avicenna J Phytomed.* 2015;5:531-539.
41. Schwenke DC et al. Alpha-tocopherol protects against diet induced atherosclerosis in New Zealand white rabbits. *J Lipid Res.* 2002;43:1927-1938.
42. Ronsein GE et al. Niacin therapy increases high-density lipoprotein particles and total cholesterol efflux capacity but not ABCA1-specific cholesterol efflux in statin-treated subjects. *Arterioscler Thromb Vasc Biol.* 2016;36:404-411.
43. Yadav R et al. Effect of extended-release niacin on high-density lipoprotein (HDL) functionality, lipoprotein metabolism, and mediators of vascular inflammation in statin-treated patients. *J Am Heart Assoc.* 2015;4:e001508.
44. Franceschini G et al. Differential effects of fenofibrate and extended-release niacin on high-density lipoprotein particle size distribution and cholesterol efflux capacity in dyslipidemic patients. *J Clin Lipidol.* 2013;7:414-422.
45. Gomaraschi M et al. Fenofibrate and extended-release niacin improve the endothelial protective effects of HDL in patients with metabolic syndrome. *Vascul Pharmacol.* 2015;74:80-86.
46. Hernaez A et al. Mediterranean diet improves high-density lipoprotein function in high-cardiovascular-risk individuals: a randomized controlled trial. *Circulation.* 2017;135:633-643.
47. Hernaez A et al. Increased consumption of virgin olive oil, nuts, legumes, whole grains, and fish promotes HDL functions in humans. *Mol Nutr Food Res.* 2019;63:e1800847.
48. Daniels J-A et al. A randomised controlled trial of increasing fruit and vegetable intake and how this influences the carotenoid concentration and activities of PON-1 and LCAT in HDL from subjects with type 2 diabetes. *Cardiovascular Diabetology.* 2014;13:16.
49. Boyer M et al. Impact of a one-year lifestyle modification program on cholesterol efflux capacities in men with abdominal obesity and dyslipidemia. *Am J Physiol Endocrinol Metab.* 2018;315:E460-E468.
50. Takata K et al. Impact of cigarette smoking cessation on high-density lipoprotein functionality. *Circ J.* 2014;78:2955-2962.
51. Gepner AD et al. Effects of smoking and smoking cessation on lipids and lipoproteins: outcomes from a randomized clinical trial. *Am Heart J.* 2011;161:145-151.
52. Park KH et al. Dysfunctional lipoproteins from young smokers exacerbate cellular senescence and atherogenesis with smaller particle size and severe oxidation and glycation. *Toxicol Sci.* 2014;140:16-25.
53. Sarzynski MA et al. Effects of increasing exercise intensity and dose on multiple measures of HDL (high-density lipoprotein) function. *Arterioscler Thromb Vasc Biol.* 2018;38:943-952.
54. Woudberg NJ et al. Exercise intervention alters HDL subclass distribution and function in obese women. *Lipids Health Dis.* 2018;17:232.
55. Koba S et al. Beneficial effects of exercise-based cardiac rehabilitation on high-density lipoprotein-mediated cholesterol efflux capacity in patients with acute coronary syndrome. *J Atheroscler Thromb.* 2016;23:865-877.
56. Mathew AV et al. Therapeutic lifestyle changes improve hdl function by inhibiting myeloperoxidase-mediated oxidation in patients with metabolic syndrome. *Diabetes Care.* 2018;41:2431-2437.

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