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Review Article

Lycopene and Cardiovascular Diseases: A Review of the Literature

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ABSTRACT

Cardiovascular diseases (CVD) are the leading causes of human disability and premature death throughout the world. Diet has a direct link with the development of CVD and so dietary change is the current approach for the prevention of CVD that is to increase the consumption of fruits and vegetables as good sources of several antioxidant phytochemicals, e.g. carotenoids. Lycopene, the most abundant carotenoid in tomatoes and tomato products has gained profuse attention in recent years for its health beneficial role, especially those related to its effects as an antioxidant and its protective role against CVD. So, the objective of this review is to assess the effect of lycopene in CVD and/or CVD risk factors studying epidemiological, clinical and biochemical data. Among twenty-three epidemiological studies investigating the association between lycopene and CVD, eight studies have found no association whereas other fifteen studies have indicated an inverse association. In case of *in vivo* and *in vitro* cell culture studies, the results are still inconsistent; some provide evidence in favor of lycopeneor tomato supplementation to reduce the prognosis of CVD and others do not support the cardio protective role of lycopene. In contrast, animal studies have provided a more vivid result, most have showna favorable effect of lycopene towards preventing CVD risk. In summary, ignoring the controversies, there lies a demand for more specific and focused research on lycopene, particularly to have a better and comprehensive understanding of lycopene's role in human health and disease for a better-quality life.

Key words: Carotenoids, lycopene, tomatoes, cardiovascular diseases.

INTRODUCTION

Worldwide, cardiovascular diseases (CVD) are the leading causes of human morbidity and mortality and approximately 31% (17.5 million) of all global deathsare attributed to CVD. [1] The current course of the diseases is expected to cause nearly 25 million deaths per year by 2020. [2] The term CVD refers to a group of disorders that includes coronary heart disease (CHD) (myocardial infarction [MI], angina pectoris, coronary insufficiency, and coronary death), cerebrovascular diseases (stroke and transient ischemic attacks [TIA]), peripheral vascular disease (PVD), congestive heart failure (CHF), hypertension, valvular and congenital heart disease. [3]

Generally, age and genetic factors are considered as irreversible CVD risk factors. Yet smoking, hypertension, abdominal obesity, abnormal lipid profile, diabetes mellitus as well as stress, low consumption of fruits and vegetables, and lack of regular physical activity are some of the modifiable factors that have been recognized as the major contributors to cardiovascular death and disability. [2, 4,5] Evidence from several epidemiological studies has concluded that diet plays a vital role in the progression of CVD, and so dietary modification has gained a profound

interest and research are now being centered on identifying the ways of dietary modification for the prevention of CVD. [6] In this context, increased consumption of a diet rich infruits and vegetables, as being a good source of various antioxidants, is often recommended by health professionals. [5,7]

Plantfoods including fruits and vegetables contain several phytochemicals, many of which are potent antioxidants, with carotenoidsas one group of lipophilic compound. [8] Carotenoids, the yellow, orange and red pigment of fruits and vegetables, havebeen one of the main hubs of research for a long periodas CVD-preventive food ingredients because of their antioxidant property. More than 600 carotenoids have been synthesized from plants, algae, and photosynthetic bacteria with about 50 compounds being employed in the human diet. Approximately 12 different carotenoids can be identified in human blood and tissues of which α-carotene, β-carotene, lycopene, β-cryptoxanthin, lutein, and zeaxanthin are the most common. [5, 9, 10] Lycopene is an unsaturated a cyclic carotenoid with 11 linear conjugated double bonds which is principally responsible for the distinctive red color of ripe tomatoes, pink grapefruit, watermelon, papaya, guava, and other fruits. Although lacking in provitamin A activity, lycopene is one of the most potent antioxidants among the dietary carotenoids. Owing to have so many conjugated dienes, lycopene has exceptionally powerful singlet oxygen quenching ability, almost twice the ability than that of β-carotene and approximately ten times that of vitamin E. [11-13] Data from epidemiological studies (cross-sectional, case-control and cohort studies),dietary intervention studies, *in vitro* cell culture studies and laboratory animal studies all suggesta supportive role of antioxidants in the prevention of many chronic diseases including CVD. These findings have generated much scientific interest in antioxidant lycopene as a source of prevention against CVD.

Keeping all this in mind, the current review is undertaken to represent the current under standing of the linkages between the red carotenoid lycopene and prevention of CVD and/or CVD risk factors, extracting information from studies conducted utilizing human as well as experimental animals as subjects.

LYCOPENE AND CARDIOVASCULAR DISEASES

Numerous studies have been conducted over the past decades to conjecturethe potential health beneficial role of carotenoids particularly lycopene.Many researcher have found that increasedingestion of tomatoes and tomato productscontaining lycopene or higher blood (plasma/serum) concentrations of lycopene is associated with the reduced risk of CVD. Despite the fact, lycopene research has got much attention after the indecisive results obtained fromthe trials with β-caroteneand vitamin E supplementation in relation to CVD. In this review, a number of human and animal studies have been evaluated to highlight the relationship between lycopene and CVD and/or CVD risk factors.

Epidemiological studies

The effect of lycopene on CVD and/or CVD risk factors have been assessedin the present reviewby studyingtwenty-three epidemiological studies (Table 1). Dietary, serum or plasma, and adipose tissue lycopene concentrationshave been measured to examine the effect of lycopene in thesedisease conditions. Among these, eight studies have found no protective effect of lycopene againstCVD and/or CVD risk factors whereas other fifteen studies have indicatedthe efficacy of lycopene to prevent the risk of CVD.

Table 1: Epidemiological studies identifying the effects of lycopene on CVDand/or CVD risk factors

Authors, year [ref]	**Study name**	**Study design, follow-up**	**Subjects[1]**	**Outcome[2]**	**Results[3]**
Gómez-Aracena et al., 1997 [14]	European Study of Antioxidants, Myocardial Infarction, and Cancer of the Breast (EURAMIC) Study, Spain	Case-control	100 vs 102 M	MI	Inverse association between adipose tissue lycopene concentration and risk of MI (OR= 0.39; 95% CI=0.13-1.19, P=0.04)
Kohlmeier et al., 1997 [15]	European Study of Antioxidants, Myocardial Infarction, and Cancer of the Breast (EURAMIC) Study	Case-control	662 vs 717 M	MI	Inverse association of adipose tissue lycopene concentration with the risk of MI (OR=0.52; 95% CI=0.33-0.82, P=0.005)
Ascherio et al., 1999 [16]	Health Professionals Follow-up Study, USA	Prospective observational 8 y	43738 M (40-75 y)	Stroke	No significant association between lycopene intake and incidence of stroke (RR=0.96; 95% CI=0.68-1.36)
Hirvonen et al., 2000 [17]	α-Tocopherol, β-Carotene Cancer Prevention (ATBC) Study, Finland	Prospective cohort 6.1 y	26593 M (50-69 y) smoker	Cerebral infarctions	Inverse association between intake of lycopene and the risks for cerebral infarction (RR=0.74; 95% CI=0.59-0.92)
McQuillan et al., 2001 [18]	Perth Carotid Ultrasound Disease Assessment Study (CUDAS), Australia	Cross-sectional	1111 (F, M) (27-77 y)	Atherosclerosis (measured by CIMT)	Inverse association between mean CIMT and plasma lycopene in women (P=0.047) but no association in men (P=0.22)
Gianetti et al., 2002 [19]	Italy	Case-control	11 vs 11 M (48-66 y)	Atherosclerosis (measured by CIMT)	Inverse relationship of plasma lycopene with IMTmax (r=-0.42; P=0.014)
Hak et al., 2003 [20]	Physicians' Health Study (PHS), USA	Prospective Nested case-control 13 y	531 vs531 M	MI	No association between plasma lycopene and risk of MI (OR=1.43; 95% CI=0.87-2.35)
Osganian et al., 2003 [21]	Nurses' Health Study (NHS), USA	Prospective 12 y	73286 F (30-55 y)	CAD	No significant association between intakes of lycopene and risk of CAD (RR=0.93; 95% CI=0.77-1.14)
Sesso et al., 2003 [22]	Women's Health Study (WHS), USA	Prospective cohort 7.2 y	39876 F (Middle- and older aged)	CVD	No significant association between lycopene and the risk of CVD (RR=0.90; 95% CI=0.69-1.17)
Dwyer et al., 2004 [23]	Los Angeles Atherosclerosis Study (LAAS), USA	Prospective	573 (F, M) (40-60 y)	Atherosclerosis (measured by CIMT)	Plasma levels of lycopene were not significantly associated with IMT progression (P=0.89)
Hak et al., 2004 [24]	Physicians' Health Study (PHS), USA	Prospective Nested case-control 13 y	297 vs297 M	Ischemic stroke	Inverse association of lycopene with the risk of ischemic stroke (OR=0.61; 95% CI=0.37-1.00)
Sesso et al., 2004 [25]	Women's Health Study (WHS), USA	Nested case-control 4.8 y	483 vs483 M	CVD	Inverse association between lycopene concentration and the risk of CVD (RR=0.66; 95% CI=0.47-0.95)
Sesso et al., 2005 [26]	Physicians' Health Study (PHS), USA	Prospective Nested case-control 13 y	499 vs499 M	CVD	No association of lycopene with the risk of CVD (RR=1.03; 95% CI=0.65-1.64)
Ito et al., 2006 [27]	Japan	Follow-up 11.9 y	3061 (F, M) (39-80 y)	CVD mortality	Significant inverse association between high serum lycopene value and the risk for CVD mortality (HR=0.73; 95% CI=0.55-0.97)
Tavani et al., 2006 [28]	Italy	Case-control 8 y	760 vs682 (F, M)	AMI	No association between lycopene and the risk of AMI (OR=1.19; 95% CI=0.82-1.70)
Hozawa et al., 2009 [29]	Coronary Artery Risk Development in Young Adults (CARDIA) Study	Prospective 20 y	4412 (F, M) (18-30 y)	Hypertension	No significant relation between lycopene and incident hypertension (RH=0.98; 95% CI=0.92-1.05)
Riccioni et al., 2009 [30]	Asymptomatic Carotid Atherosclerotic Disease in Manfredonia (ACADIM) Study, Italy	Cross- sectional	640 F, M	Atherosclerosis (measured by CIMT)	Plasma lycopene was significantly lower in participants with carotid atherosclerosis (P<0.001)
Kim et al., 2010 [31]	Cardiovascular-Aging Control Study, Korea	Cross-sectional	264 F (31-75 y)	Arterial stiffness (measured by baPWV)	Inverse relationship between circulating lycopene and baPWV (β=-0.221;95%CI=-0.215;-0.012, P=0.029)
Karppi et al., 2011 [32]	Kuopio Ischaemic Heart Disease Risk Factor (KIHD) Study	Cohort	1212 M (61-80 y)	Atherosclerosis (measured by CIMT)	Inverse association of plasma lycopene concentrations with carotid atherosclerosis (r=-0.138; P<0.001)
Yeo et al., 2011 [33]	Korea	Cross sectional 1 y	299 M	Arterial stiffness (measured by baPWV)	Inverse correlation of baPWV with serum lycopene (r=-0.136; P<0.05)
Karppi et al., 2012 [34]	Kuopio Ischaemic Heart Disease Risk Factor (KIHD) Study	Prospective 12.1 y	1031 M (46-65 y)	Stroke	Inverse association between serum lycopene and the risk of any stroke (HR=0.45; 95% CI=0.25-0.95, P=0.036)
Xu et al., 2012 [35]	Beijing Atherosclerosis Study	Case-control	40 vs 40	Atherosclerosis	Lycopene was inversely associated with VCAM-1 (P=0.011) and LDL (P=0.046)

Table 1: Continued….					
Biddle et al., 2013 [36]	Kentucky, Indiana and Georgia	Prospective 1y	212 (M, F) Patients with HF	HF	Higher lycopene intake was associated with longer cardiac event-free survival compared with lower lycopene intake (P=0.003) in patients with HF

[1]M: Male, F: Female; y: Year. [2]AMI: Acute myocardial infarction, baPWV: Brachial-ankle pulse wave velocity, CAD: Coronary artery disease, CIMT: Carotid Intima Media Thickness; HF: Heart Failure, IMTmax: Carotid maximum intima-media thickness, MI: Myocardial infarction. [3]β:Regression coefficients, HR: Hazard ratio, LDL: Low-density lipoprotein, OR: Odds ratio, r: Correlation coefficient, RH=Relative Hazards, RR: Relative risk, VCAM-1: Vascular cell adhesion molecule.

Table 2: *In vivo* intervention studies investigating the effects of lycopene (or tomatoes or tomato products) supplementation on CVD and/or CVD risk factors

Authors, year [ref]	Subjects[1]	Lycopene supplementation			Results[2]
		Form	Dose (mg/day)	Duration	
Agarwal and Rao, 1998 [37]	19 (10 M, 9 F) (25-40 y)	Spaghetti sauce	39.2	1 week	Significant decrease in serum lipid peroxidation and LDL oxidation
		Tomato juice	50.4		
		Lycopene capsule	75		
Bub et al., 2000 [38]	23 M (27-40 y)	Tomato juice	40	2 weeks	18% reduction in LDL oxidation (P<0.001) Reduction in lipid peroxidation
Carroll et al., 2000 [39]	47 (25 F, 22 M) (≥65 y)	Lycopene capsule	13.3	12 weeks	No reduction or delay of LDL oxidation (P=0.397)
Hininger et al., 2001 [40]	175 M (25-45 y)	Lycopene capsule	15	12 weeks	No significant effect on LDL oxidation or LDL polyunsaturated/saturated fatty acid ratio No change in antioxidant enzyme (SOD, GSH-Px) activities
Visioli et al., 2003 [41]	12 F (22-38 y)	Different tomato products (raw, sauce, and paste)	8	3 weeks	Significant reduction in LDL oxidation (P<0.001) No significant change of plasma antioxidant capacity Significantly decrease in urinary excretion of 8-*epi*-$PGF_{2\alpha}$
Riso et al., 2004 [42]	12 F	Different tomato products (raw, sauce, and paste)	8	3 weeks	24% reduction in DNA damage (P<0.05) No significant reduction in lipid peroxidation (measured by MDA)
Tyssandier et al., 2004 [43]	20 F (20-40 y)	Tomato puree	13.6	3 weeks	No significant effect on plasma TAOC
Bub et al., 2005 [44]	22 M	Tomato juice	37	2 weeks	Significant reduction in lipid peroxidation No effect on LDL oxidation
Porrini et al., 2005 [45]	26 (M, F)	Lyc-O-Mato	5.7	26 days	Significantly reduction (about 42%) in DNA damage (P<0·0001) in lymphocytes subjected to oxidative stress
Bose and Agrawal, 2006 [46]	30 (M, F) (35-55 y) type 2 diabetic patients	Ripe tomatoes (cooked)		60 days	Significant improvement (P<0.001) in antioxidant enzymes (SOD,GSH-Px, GR and GSH)levels and decrease in lipid peroxidation (MDA) rate No significant changes in lipid profile (TG, HDL, LDL)
Engelhard et al., 2006 [47]	31 (M, F) (30-70 y) grade I hypertension	Lyc-O-Mato	15	8 weeks	Significant decrease in systolic (P<0.001) and diastolic (P<0.05) blood pressure No significant changes in lipid parameters Significant decrease in lipid peroxidation
Madrid et al., 2006 [48]	17 (9 M, 8 F)	Tomato juice	18	7 days	No significantly change in TRAP, catalase and SOD Significant increase in HDL cholesterol (P<0.002)
Paterson et al., 2006 [49]	36 (12 M, 24 F) (20-70 y)	Tomato soup	10	4 weeks	No effect on plasma antioxidant status No effect on plasma total, HDL, and LDL cholesterol level
Riso et al., 2006 [50]	26 (F, M)	Lyc-O-Mato	5.7	26 days	34.4% reduction in TNF-αproduction by whole blood No significant lymphocyte DNA damage
Sánchez-Moreno et al., 2006 [51]	12 (6 M, 6 F)	Tomato soup (gazpacho)		14 days	Significantly decrease of 8-*epi*-$PGF_{2\alpha}$, PGE_2 and MCP-1 concentrations No effect on TNF-α, IL-1β and IL-6
Zhao et al., 2006 [52]	37 (50-70 y) post-menopausal women	Lycopene capsule	4 or 8	56 days	Significant reduction in endogenous DNA damage (P<0.01)
Blum et al., 2007 [53]	103 (35 M, 68 F)	Tomato		30 days	No significant change of inflammatory markers (hs-CRP, E-selectin and ICAM-1)
Bose and Agrawal, 2007 [54]	30 (M, F) (35-55 y) grade I hypertensive patients	Ripe tomatoes (cooked)	25	60 days	Significant reduction in MDA levels indicating a lower rate of lipid peroxidation (P<0.001) Significant increase in levels of antioxidant enzymes (SOD, glutathione reductase, GSH-Px) (P<0.001) No significant changes in lipid profile (P>0.10)
Neyestani et al., 2007 [55]	35 (M, F) (35-70 y) type 2 diabetic patients	Lycopene	10	8 weeks	Significant decrease in serum MDA level while increase in TAOC/MDA indicating attenuation of oxidative stress
Silaste et al., 2007 [56]	21 (15 F, 6 M) (20-49 y)	Tomato juice and tomato ketchup	27	3 weeks	Significant reduction in plasma total and LDL cholesterol level Significant decrease in LDL oxidation
Denniss et al., 2008 [57]	27 (18 M, 9F)	Lyc-O-Mato	80	1 week	No effect on biomarkers of vascular oxidative stress (measured by MDA) and inflammation (measured by CRP)

Table 2: Continued….

Devaraj et al., 2008 [58]	77 (19 M, 58 F)	Lycopene capsule	6.5, 15 or 30	8 weeks	Significant decrease in DNA damage by the comet assay (P<0.007), and a significant decrease in urinary 8-OHdG versus baseline (P<0.0002), with 30 mg lycopene/day No significant inter- or intra-group differences for lipid profile, or other biomarkers of lipid peroxidation at any dose/time point
Lee et al., 2009 [59]	10 M	Tomato sauce	30	48 hours	No change in plasma levels of F_2-isoprostanes, hydroxy-eicosatetraenoic acid products, allantoin and urinary 8-OHdG Significant decrease in urinary F_2-isoprostanes level (P<0.05)
Markovits et al., 2009 [60]	16 (8 M, 8F)	Lyc-O-Mato	30	4 weeks	No change in the markers of inflammation and oxidation products (CRP, IL-6, TNF-α, conjugated dienes)
Paran et al., 2009 [61]	50 (26 M, 24 F) (46-66 y) grade I hypertensive patients	Lyc-O-Mato	15	6 weeks	Significant reduction of systolic (P<0.001) and diastolic (P=0.001) blood pressure
Ried et al., 2009 [62]	36 (19 M, 17 F) pre-hypertensive patients	Lyc-O-Mato	15	8 weeks	No significant changes of blood pressure over time within groups and between groups in pre-hypertensive patients
Kim et al., 2011 [63]	126 M (22-57 y)	Lycopene	6 or 15	8 weeks	Significant dose dependent decrease in lymphocyte DNA damage and increase in plasma SOD activity Significant decrease in systolic blood pressure (P=0.037), plasma concentrations of ICAM-1 (P=0.008) and VCAM-1 (P=0.02), and serum concentrations of hs-CRP (P=0.046), and increase in plasma LDL particle size with 15 mg lycopene only
Shidfar et al., 2011 [64]	32 M (40-60 y) type 2 diabetic patients	Raw tomato		8 weeks	Significant decreases in systolic (P=0.0001) and diastolic (P=0.0001) blood pressure Significant increase in apoA-1 (P<0.013)
Stangl et al., 2011 [65]	31 F non-smoking post-menopausal	Tomato puree	46	24 h and 7 days	No effects on endothelium-dependent or -independent dilation of the brachial artery on acute or long term consumption
Burton-Freeman et al., 2012 [66]	25 (13 M, 12 F) (19-35 y)	Tomato paste	27	6 h	Significantly reduction in serum oxidized LDL cholesterol and IL-6 level No effect on hs-CRP and TNF-α
Thies et al., 2012 [67]	225 (94 M, 131 F) (40-65 y) moderately overweight	Tomato Lycopene capsule	32-50 10	12 weeks	No significant change in inflammatory markers, lipid concentrations and arterial stiffness
Xaplanteris et al., 2012 [68]	19 (8 M, 11 F) (26-52 y)	Tomato paste	33.3	14 days	Significant increase in FMD leading to improved endothelial function (P<0.05) Significant decreased in TOS compared with baseline (P=0.038)
Abete et al., 2013 [69]	30 (9 M, 21 F) (18-50 y)	Tomato sauce	12.3 or 27.2	4 weeks	Significant reduction in oxidized-LDL cholesterol levels (P<0.05) in high- lycopene tomato sauce consumption
Cuevas-Ramos et al., 2013 [70]	50 (9 M, 41 F) overweight	Tomato (uncooked)		4 weeks	Significant increase in serum HDL cholesterol levels in overweight women (P<0.0001)
Ghavipour et al., 2013 [71]	106 F (20-40 y) obese or overweight	Tomato juice	37	20 days	Significant decrease in IL-8 and TNF-α in overweight only Significant decrease in serum IL-6 concentration in obese only
McEneny et al., 2013 [72]	54 (M, F) (40-65 y) moderately overweight	Tomato Lycopene	32-50 10	12 weeks	Significant decrease in systemic SAA level leading to reduced inflammation and restoring some of HDL's antiatherogenic properties
Tsitsimpikou et al., 2014 [73]	27 (24 M, 3 F)	Tomato juice	5	2 months	Significantly decrease of TNF-αlevels (P=0.021) Significant (P=0.026) improvement in the endothelial function (measured by ADMA) Significant decrease in serum LDL-cholesterol (P<0.001) and a slight increase in HDL cholesterol levels (P=0.049)
Burton-Freeman et al., 2016 [74]	53 (21-70 y) overweight or obese	Tomato		6 weeks	Significant decrease in diastolic blood pressure but no effect on systolic blood pressure No effect on plasma lipid profile (TG, LDL and HDL) or inflammatory markers (hs-CRP, TNF-α, IL-6)

[1]M: Male, F: Female, y: Year. [2]8-*epi*-$PGF_{2\alpha}$: 8-*epi*-prostaglandin $F_{2\alpha}$, 8-OHdG: 8-hydroxy deoxoguanosine, ADMA: Asymmetric dimethyl arginine, apoA-1: Apolipoprotein A-1, CRP: C-reactive protein, FMD: Flow-mediated dilatation, GSH-Px: Glutathione peroxidase, GR: Glutathione reductase, HDL: High-density lipoprotein, hs-CRP: High sensitivity C reactive protein, ICAM-1: Intercellular adhesion molecule-1, IL-1β: Interleukin-1β, IL-6: Interleukin-6, IL-8: Interleukin-8, MCP-1: Monocyte chemotactic protein, MDA: Malondialdehyde, PGE_2: Prostaglandin E_2, SAA: Serum amyloid A, SOD: Superoxide dismutase, TAOC: Total antioxidant capacity, TNF-α: Tumor necrosis factor alpha, TOS: Total oxidative status, TRAP: Total peroxyl radical trapping.

Human interventional studies

To date, numerous interventional (both *in vivo* and *in vitro*) studies have been published investigating the effects of lycopene (or tomatoes or tomato products) supplementation on CVD and/or CVD risk factors. Studies on the supplementation with lycopene, singly or in combination with other carotenoids and nutrients, for variable periods of time were performed in order to evaluate the possible effects on CVD and/or related pathophysiological factors or markers.

In vivo studies. A total of thirty-eight clinical trials have been analyzed in this review on the effect of dietary supplementation with lycopene, or tomatoes and tomato products on CVD and/or CVD risk factors (Table 2). The supplements used as lycopene source were raw tomato (both cooked and uncooked), tomato juice, tomato paste, tomato sauce/ketchup, tomato puree, tomato soup, and lycopene capsule (as Lyc-O-Mato, which is a tomato lycopene complex containing lycopene and several phytonutrients including phytoene, phytofluene, β-carotene, tocopherols, and phytosterols).In these studies, the duration of lycopene supplementation was as low as 6 h to 12 weeks long. Lycopene doses ranged from 4 mg/day lycopene (for 8 weeks) to 80 mg/day (for 1 week). The biomarkers assessed as emerging CVD risk factors were oxidative stress and antioxidant enzyme activity, inflammation, blood pressure, endothelial function, lipid profile and lipid peroxidation. Among the analyzed studies, some provided evidence in favor of lycopeneor tomato supplementation to reduce the prognosis of CVD and others did not support the cardioprotective effect of lycopene.

In vitro studies. Advances in basic and clinical science in the last years have elicited *in vitro* antioxidant potency of lycopene derived from foods or supplements. In the present review, the role of lycopene in the different risk factors that contribute to CVD has been discussed studying eight such *in vitro* cell culture studies (Table 3). Different studies examined different types of human cells with different lycopene doses. Investigation of these studies illuminated that lycopene might have a preventive role in the development of CVD by reducing oxidative stress, inflammation, platelet aggregation, expression of HMG-CoA reductase, intracellular cholesterol levels and lipid peroxidation in a dose- and time-dependent manner in the examined cells.

Table 3: *In vitro* cell culture studies assessing the potency of lycopene in the different risk factors of CVD

Authors, year [ref]	Cell type	Lycopene dose (μmol/L)	Results[1]
Hsiao et al., 2005 [75]	Human platelet	2-12	Dependent inhibition of platelet aggregation by inhibiting the activation of phospholipase C, and activating cyclic GMP/nitrate formation
Safari, 2007 [76]	Human plasma	0-200	Significant inhibition of the copper-catalyzed oxidation of LDL in a dose-dependent manner (P<0.01) Suppression of the formation of lipid peroxides and TBARS
Hung et al., 2008 [77]	Human umbilical vein endothelial cells (HUVECs) and THP-1 monocytes		Inhibition of TNF-α-induced NF-κB activation, ICAM-1 and VCAM-1 expression, and monocyte-endothelial interaction No effect on COX-2 and PECAM-1 expression
Tang et al., 2009 [78]	Vascular endothelial cells (ECV304 cells)	0.2-20	Protection against oxidative attacks by H_2O_2 (measured by reduced MDA level) Significant reduction of the apoptosis ration of oxidative injured cells Downregulation of the expression of p53 and caspase-mRNA induced by H_2O_2
Palozza et al., 2010 [79]	Human THP-1 macrophages	0.5-2	Significant reduction of the increase in ROS production and in 8-OHdG formation induced by the oxysterol in a dose-dependent manner Significant inhibition of 7-KC-induced apoptosis by limiting caspase-3 activation
Palozza et al., 2011 [80]	Human THP-1 macrophages	0.5-2	Reduction of the intracellular total cholesterol content through the reduction of HMG-CoA reductase expression
Di Tomo et al., 2012 [81]	Human umbilical vein endothelial cells (HUVECs)	2.5	Significant reduction of TNF-α-induced inflammation
Sung et al., 2015 [82]	Human umbilical vein endothelial cells (HUVECs)	3-10	Inhibition of cyclic strain-induced ET-1 expression through the suppression of ROS generation and induction of HO-1

[1]7-KC: 7-ketocholesterol, COX-2: Cyclooxygenase-2, ET-1: Endothelin-1, H_2O_2: Hydrogen peroxide, HMG-CoA: 3-hydroxy-3-methylglutaryl-coenzyme A, HO-1: Heme oxygenase-1, PECAM-1: Platelet-endothelial cell adhesion molecule, ROS: Reactive oxygen species, TBARS: Thiobarbituric acid-reactive substances.

Animal studies

Animal models used to conduct research are typically inbred animals, thus reducing genetic variation and producing clearer results. Here, available evidence for a direct regulation of lycopene on the development of the risk of CVD has been reviewed using results from the following fourteen animal studies (Table 4). Type of animal models, lycopene doses and duration of the supplementation were different among the studies. Findings of all of the studies revealed a favorable effect of lycopene towards preventing CVD risk except Frederiksen et al., study where Male Watanabe Heritable Hyperlipidemic (WHHL) rabbits were examined for a long period (16 weeks) and did not find any significant effect of lycopene on the markers of CVD.

Table 4:Animals studies showing the efficacy of lycopene supplementation on CVD risk factors

Authors, year [ref]	Animal model	Lycopene supplementation		Results[1]
		Dose/day	Duration	
Hassan and Edrees, 2004 [83]	Male*Rattusnorvegicus*	1 mg/kg	4 weeks	Significant decrease in serum total lipids, total cholesterol and LDL cholesterol level
Bansal et al., 2006 [84]	Male Albino Wistar rats	1 mg/kg	31 days	Significant reduction (P<0.001) of ischemia-reperfusion induced lipid peroxidation (measured by reduction in MDA levels) Significant increase in level of GSH content (P<0.05) and antioxidant enzyme GSH-Px (P<0.001)
Sahin et al., 2006 [85]	Female Japanese quail	100 mg/kg	70 days	Significant decrease in serum MDA level (P<0.05) Decrease in serum cholesterol level (P<0.05)
Frederiksen et al., 2007 [86]	Male Watanabe Heritable Hyperlipidemic (WHHL) rabbits	15 mg/100 g diet	16 weeks	No effect on cholesterol and TG levels in total plasma, lipoprotein fractions and on aortic atherosclerosis No effect on oxidation of lipids in unfractionated plasma
Hu et al., 2008 [87]	Male New Zealand white rabbits	4 mg/kg and 12 mg/kg	4 and 8 weeks	Decrease in the levels of total cholesterol, total TG, LDL cholesterol, malonaldehyde, oxidized LDL and IL-1 increased and total antioxidant capacity and nitric oxide (P<0.05) Reduction in the formation of atherosclerotic plaques in the aorta
Kuhad et al., 2008 [88]	Male Albino mice of Laca strain	1, 2 and 4 mg/kg	4 and 8 weeks	Significant dose dependent decrease in TNF-α levels and serum nitrite levels in diabetes mice
Verghese et al., 2008 [89]	Male New Zealand white rabbits	42.6, 85.2, and 127.8 ppm	12 weeks	Decrease in serum total cholesterol and LDL cholesterol levels and increase in HDL cholesterol level (P≤0.05) Reduction in hepatic HMG-CoA reductase activity (P≤0.001) and ACAT activity (P≤0.05) 64.3% reduction in the formation of atherosclerotic plaques in the aorta
Verschuren et al., 2011 [90]	Female ApoE*3Leiden transgenic mice	3.75 mg	6 weeks	Significant decrease in cholesterol and TG level in plasma
Lorenz et al., 2012 [91]	Male New Zealand White (NZW) rabbits	5 mg/kg	4 weeks	Significant reduction in serum total and LDL cholesterol levels as well as cholesteryl ester in the aorta
Mohamadin et al., 2012 [92]	Adult male Sprague-Dawley rats	4 mg/kg	21 days	Significant amelioration of lysosomal membrane damage as well as the alterations in cardiac enzymes, lipid profile and oxidative stress markers in ISO rats
Ojha et al., 2013 [93]	Wistar male albino rats	0.5, 1.0 and 1.5 mg/kg	30 days	Significant (P<0.05) attenuation of ISP-induced cardiac dysfunction evidenced by improved SAP, DAP, MAP, (±)LVdP/dt (at 1.0 and 1.5 mg/kg doses), and HR (at all doses) Significant (P< 0.05) prevention of the depletion of antioxidants (SOD, CAT, GSH-Px and GSH), myocyte injury marker enzymes (CK-MB and LDH) Inhibition of lipid peroxidation and MDA formation in the heart
Wang et al., 2014[94]	Male Sprague-Dawley rats	40 mg/kg	28 days	Improvement in the cardiac function and ventricular remodeling by inhibition of p38 activation and MMP-9 expression
Martin-Pozuelo et al., 2015 [95]	Male Sprague-Dawley rats	105 mg/kg	5 weeks	Significant improvement in the plasma HDL level (P<0.05)
Vilahur et al., 2015[96]	Female swine	21.5 mg	10 days	Reduction in oxidized LDL concentration Increase in endothelial eNOS expression and activity Improvement in HDL functionality

[1](±)LVdP/dt: Peak positive and negative left ventricular end-diastolic pressure development,ACAT: Acyl-CoA-cholesterol acyltransferase, CAT: Catalase, CK-MB: Creatine phosphokinase-MB, DAP: diastolic arterial blood pressure, eNOS: Endothelial nitric oxide synthase, GSH: Reduced glutathione, HR: Heart rate, ISP: Isoproterenol, LDH: Lactate dehydrogenase, LVEDP: Left ventricular end-diastolic pressure, MAP: Mean arterial blood pressure, MMP-9: Matrix metalloproteinase 9, SAP: Systolic arterial blood pressure.

CONCLUSION

It has been demonstrated that diet plays a dual role both in the development and also in the prevention of many chronic diseases like CVD. As fruits and vegetables are great sources of many antioxidants,

higher dietary intake is advised nowadays to prevent the development of heart diseases. So, the area of interest of this review was on examining the available studies assessing the effectiveness of lycopene on CVD and/or CVD risk factors. Nonetheless, there lies incongruity between epidemiological and human intervention trials, there is still some promising evidence for a role of lycopene for the prevention of CVD. Discrepancies occurred may be due to age and gender factors, number of subjects, duration of studies, presence or absence of other nutrients (e.g. vitamin A, E, and C) etc. On the other hand, a clearer relationship between lycopene intake and reduction of risk of CVD was found in animal studies. However, the evidence found so far is mainly suggestive. All of the studies have also failed to provide any recommendation on optimal dose or amount of lycopene or tomato and tomato products consumption at individual or population level.

In a nutshell, research with lycopene needs to be expanded, along with other natural products having health beneficial effect, and there exist ample opportunities for that. More specific and focused research, therefore, will provide a better and comprehensive understanding of lycopene's role not only in CVD but also in other chronic diseases for a better-quality life.

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