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REVIEW

# Lycopene and heart health

*Volker Böhm*

Institute of Nutrition, Friedrich Schiller University Jena, Jena, Germany

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Cardiovascular diseases (CVDs) are the leading causes of human morbidity and mortality in developed countries. Specific biomarkers in this context are markers of inflammation, lipid status, thrombosis and oxidative stress. One recommendation for CVD prevention is to increase consumption of fruits and vegetables as good sources of secondary plant products, e.g. carotenoids. This review aimed to show linkages between lycopene, one main carotenoid in the human diet, and prevention of heart diseases by looking for epidemiological data, results from in vitro experiments and results from in vivo studies (animal studies and human intervention trials). In addition, patents and products within the context of lycopene and CVD prevention will be discussed with a special emphasis on health claims. Epidemiological data, in vitro data and results from animal experiments partly showed promising preventive mechanisms of lycopene. In contrast, until now, human intervention studies mostly failed to show any CVD prevention. However, there is still an encouraging situation, giving hints for antioxidant as well as anti-inflammatory effects of lycopene. These mechanisms could be the background for cardio-protective effects of tomatoes and tomato products. In summary, there are a lot of investigations needed in the future to give reliable results to establish these CVD-preventive effects.

**Keywords:**
Antioxidant / Atherosclerosis / Cardiovascular diseases / Inflammation / Lipid status

## 1 Introduction

Heart diseases are the leading causes of human morbidity and mortality in developed countries. Cardiovascular diseases (CVDs) accounted for 30% (17.5 millions) of all deaths globally according to WHO data from 2005 [1]. Beside genetic factors and age (non-modifiable CVD risk factors) modifiable risk factors (hypertension, smoking, abdominal obesity, abnormal lipid profile, diabetes mellitus as well as low consumption of fruits and vegetables and lack of regular physical activity) are the major contributors to cardiovascular morbidity and mortality. Oxidative stress and endothelial dysfunction are two pathophysiologically CVD-relevant processes; http://www.who.int/mediacentre/factsheets/fs317/en/print.html [2]. Diet changes and their effects on CVD incidence have long been investigated. One recommendation in this context is to increase consumption of fruits and vegetables, being good sources of various antioxidants [3].

Carotenoids, the yellow, orange and red coloured pigments of several fruits and vegetables are one class of compounds being discussed for a long time as CVD-preventive food ingredients [4]. More than 750 carotenoids have been characterised with approximately 50 compounds being present in the human diet. Analysing human blood plasma samples as well as tissue samples, 10–15 carotenoids are determined of which lutein, zeaxanthin, β-cryptoxanthin, α-carotene, β-carotene and lycopene are the main compounds [5, 6]. Lycopene is an acyclic carotenoid with 11 conjugated

**Correspondence:** Dr. Volker Böhm, Institute of Nutrition, Friedrich Schiller University Jena, Dornburger Str. 25-29, D-07743 Jena, Germany
**E-mail:** volker.boehm@uni-jena.de
**Fax:** +49-3641-949702

**Abbreviations: baPWV,** brachial-ankle pulse wave velocity; **b.w.,** body weight; **CAT,** catalase; **CRP,** C-reactive protein; **CVD,** cardiovascular disease; **DNA,** deoxyribonucleic acid; **EFSA,** European Food Safety Authority; **GSH-Px,** glutathione peroxidase; **HMG-CoA,** 3-hydroxy-3-methylglutaryl-coenzym-A; **hs,** high sensitivity; **ICAM,** intercellular adhesion molecule; **MDA,** malondialdehyde; **mRNA,** messenger ribonucleic acid; **oxLDL,** oxidized low density lipoprotein; **PDGF,** platelet-derived growth factor; **SMC,** smooth muscle cell; **SOD,** super oxid dismutase; **ROS,** reactive oxygen species; **TNF-α,** tumour necrosis factor α; **t. p.,** tomato paste; **VCAM,** vascular cell adhesion molecule; **WSTC,** water-soluble tomato concentrate

 

double bonds, being responsible, e.g. for the red colour of tomatoes. Tomatoes and tomato products are the main food sources of lycopene in our diet. In addition, pink grape fruits, papayas, guavas, rosehip products and sea buckthorn berry products contain lycopene. As oxidation of cholesterol in arteries is discussed as one mechanism leading to CVD, the antioxidant activity of carotenoids has been investigated as one preventive action of carotenoids [4]. Lycopene has been shown in in vitro experiments as a very efficient singlet oxygen quencher with approx. twice the activity of β-carotene [7]. Lycopene was also able to scavenge other reactive oxygen species (ROS) as superoxide radicals, peroxyl radicals, hydroxyl radicals [7]. Own in vitro investigations using different assay systems showed a high ferric reducing activity (2.1 times higher than α-tocopherol) as well as a good peroxyl radical scavenging activity (13.3 times higher than α-tocopherol) for lycopene compared to other carotenoids [8].

Recently, Kampoli et al. [9] reviewed the roles of specific biomarkers that have been implicated in premature atherosclerosis. Due to this review, the ideal biomarker that will be able to facilitate the clinical diagnosis of CVD should have the following characteristics: highly sensitive, specific, reliable, accessible, standardised, cost effective and easily interpretable by clinicians. The paper [9] presents the most promising biomarkers used in risk assessment of premature atherosclerosis. Molecules implicated in atherosclerotic processes are, e.g. intercellular adhesion molecule (ICAM)-1, vascular cell adhesion molecule (VCAM)-1, several interleukins (IL-1, IL-3, IL-8, IL-18) and tumour necrosis factor α (TNF-α). The most extensively studied biomarker of inflammation in CVD is C-reactive protein (CRP), high-sensitivity (hs) assays (hs-CRP) are widely available. A specific range of CRP levels is used to predict CVD: in case of hs-CRP level >1.0 mg/L there is a low risk of developing CVD, levels between 1.0 and 3.0 mg/L are linked to an average risk, CRP levels >3.0 mg/L indicate high risk. However, recent studies demonstrated that IL-6 and TNF-α are stronger predictors for CVD than CRP. Apolipoproteins B and A-I are the main lipid metabolic markers being used, in particular their ratio. The two major thrombotic markers are fibrinogen and homocysteine. All these markers are discussed to be important in risk assessment as inflammation, thrombosis and oxidative stress are processes with crucial roles in pathogenesis of atherosclerosis.

The aim of this paper is to present the current situation of linkages between the carotenoid lycopene and prevention of heart diseases, discussing epidemiological data and in vitro experiments as well as in vivo studies. Finally, a conclusion on the importance of lycopene in heart health will be given.

## 2 Epidemiological studies

Various epidemiological studies over the past decades showed protection against many chronic diseases, including CVD, due to high consumption of plant foods. Numerous phytochemicals are contained in plant foods, many of which are potent antioxidants, with carotenoids as one group of lipophilic antioxidants [10]. Recently, 139 Cretan (Greece) men aged 79 years and over were compared to men from Zutphen (The Netherlands). The Cretan men had nearly fourfold higher mean levels of lycopene as well as a lower level of oxidative stress and higher levels of antioxidants in plasma than men of the same age from Zutphen [11]. Karppi et al. [12] analysed serum samples of 349 subjects on concentrations of conjugated dienes in LDL, being one marker of lipid oxidation. The values were significantly lower in men compared to women. Lycopene content in plasma was significantly negatively associated with content of conjugated dienes. Thus, dietary carotenoids contributed significantly to lowered LDL oxidative modification in vivo. Kim et al. [13] analysed serum samples of 264 healthy Korean women on their contents of lycopene. In addition, arterial stiffness as a possible marker involved in the pathophysiology of CVD was assessed by brachial-ankle pulse wave velocity (baPWV). Serum lipid profile, hs-CRP and contents of oxidized low density lipoprotein (oxLDL) were also analysed. A negative correlation was found between lycopene and oxLDL and also between lycopene and baPWV. Thus, lycopene may be responsible for a reduced oxidative modification of LDL, being possibly one mechanism by which lycopene could reduce arterial stiffness and the risk of CVD. A total of 299 Korean men were investigated on interrelationship between arterial stiffness, antioxidant status and the risk of metabolic syndrome. The authors analysed beside other parameters, baPWV, content of lycopene, lipid profile and oxLDL. baPWV was inversely correlated with lycopene content in serum. A negative correlation was also seen between lycopene and oxLDL. Thus, an interrelationship was shown between circulating lycopene, baPWV and metabolic syndrome [14]. Within a follow-up period of 11.9 years in another study, 3061 participants were asked to fill in a questionnaire and to give serum samples. Lycopene contents in serum tended to be lower for those who had died due to CVD than for those who survived [15]. A case-control study with 760 cases and 682 controls showed a decreased risk of acute myocardial infarction with increasing intake of α-carotene, β-carotene and β-cryptoxanthin but no association for lycopene [16]. The CARDIA Study (Coronary Artery Risk Development in Young Adults) with 4580 participants showed that those people with higher lycopene contents tended to have less healthy lifestyles. Serum total and individual carotenoids, with the exception of lycopene, were inversely associated with markers of inflammation, oxidative stress and endothelial dysfunction [17]. The Minnesota Heart Survey Study with 5369 men and 6070 women used a 24-h dietary recall. The authors developed a *Heart Disease Prevention Index*. This index improved between 1980/1982 and 2000/2002: for men by

 

2.58 points (8.3%) from 31.14 to 33.72 and for women by 2.44 points (7.9%) from 30.97 to 33.41. Thus, overall diet quality has moderately improved. However, improvement has plateaued and levelled off during the last 5-year period that was studied. Regarding the carotenoids, only uptake of β-carotene, lutein, zeaxanthin and β-cryptoxanthin significantly increased from 1980/1982 to 2000/2002, but not consumption of lycopene [18]. So, controversial epidemiological data exist regarding the CVD-preventive effects of lycopene.

## 3 In vitro experiments

In cell experiments with human umbilical vein endothelial cells and THP-1 monocytes, lycopene significantly inhibited TNF-α-induced ICAM-1 and VCAM-1 expression. Lycopene also inhibited TNF-α-induced NF-κB activation and monocyte-endothelial interaction [19]. The effects of lycopene on oxidative injury and apoptosis in endothelial cells following exposure to $H_2O_2$ was investigated by Tang et al. [20]. They used human vascular endothelial cells (ECV304 cells) and divided them into six groups: control group, $H_2O_2$ group, three lycopene groups (0.2/2/20 μM) and a drug control group (probucol). Cells in the control group were incubated for 24 h under normal growth conditions. Cells in the other groups were incubated for 24 h with medium containing 400 μM $H_2O_2$. Within the lycopene groups, the cells were preincubated for 30 min with different concentrations of lycopene, followed by a 24-h incubation with 400 μM $H_2O_2$. In the drug control group, cells were preincubated with 40 μM probucol instead of lycopene. Pre-treatment with lycopene dose-dependently decreased malondialdehyde (MDA) contents in $H_2O_2$-treated cells. Lycopene also significantly reduced the number of cells undergoing apoptosis in response to $H_2O_2$. Oxidative stress can induce p53 and caspase3, two important factors that lead to apoptosis. Lycopene pre-treatment significantly inhibited the upregulation of p53 messenger ribonucleic acid (mRNA) and caspase3 mRNA. Thus, due to these results protecting endothelial cells from oxidative injury possibly could be one of the potential mechanisms underlying the cardiovascular-related beneficial effects of lycopene.

Lycopene (0.5–2 μM) dose-dependently reduced intracellular content of total cholesterol in THP-1 cells. This effect was due to a reduction in expression of 3-hydroxy-3-methylglutaryl-coenzym-A (HMG-CoA) reductase, an enzyme promoting the deacylation of HMG-CoA to mevalonate [21]. As hypercholesterolemia is one of the most important risk factors for atherosclerosis, these results imply a potential role of lycopene in attenuating foam cell formation and thus in CVD risk reduction. Lycopene (0.5–2 μM) also dose-dependently reduced 7-ketocholesterol-induced ROS production and 8-hydroxydeoxyguanosine formation in human THP-1 macrophages. In addition, lycopene was able to counteract 7-ketocholesterol-induced apoptosis by limiting caspase-3 activation [22].

Abnormal vascular smooth muscle cell (SMC) proliferation and growth factors such as the platelet-derived growth factor (PDGF) play an important role in development and progression of CVDs. Lycopene inhibited PDGF-BB induced signalling in SMCs of rats. Lycopene directly bound to PDGF-BB and inhibited PDGF-BB-SMC interaction. Lycopene (2–10 μM) inhibited PDGF-BB-induced SMC proliferation [23]. Intravascular thrombosis is a factor in the generation of CVD. Lycopene (2–12 μmol/L) concentration-dependently inhibited platelet aggregation in human platelets and the ATP-release reaction stimulated by agonists (collagen, arachidonic acid). These results may imply that tomato-based foods are especially beneficial in the prevention of platelet aggregation and thrombosis [24].

The role of lycopene in the different phases of the atherosclerotic process in cell culture studies was discussed in a recent review [25]. One important determinant is chronic or repetitive endothelial injury, causing intimal thickening. Recent investigations showed that lycopene may be protective by limiting smoke-induced oxidative stress and by controlling molecular pathways involved in cell proliferation, differentiation, apoptosis and inflammation. Another important risk factor for atherosclerosis is hypercholesterolaemia. Lycopene was able to reduce the expression of HMG-CoA reductase in a dose- and time-dependent manner in THP-1 cells, being accompanied by a reduction in intracellular cholesterol levels. As ROS play a key role in the pathogenesis of atherosclerosis, it was CVD-relevant to show that lycopene and tomato extracts were able to decrease rates of LDL oxidation. Comparing lycopene alone and combinations of antioxidants, lycopene often showed lower activity protecting LDL towards oxidation than mixtures of compounds. In addition, physiologically relevant lycopene concentrations were able to counteract the oxidative processes triggered by 7-ketocholesterol. Increased levels of oxysterols were recently associated with an increased risk of atherosclerosis. Furthermore, lycopene may reduce macrophage foam cell formation in response to modified LDL by decreasing lipid synthesis and down-regulating the activity and expression of scavenger receptors. Several recent studies have reported the reduction of pro-inflammatory cytokines by lycopene. Lycopene might also be important in inhibiting SMC proliferation [25] as Lo et al. [23] showed inhibition of PDGF-BB induced migration and proliferation of rat SMCs.

Most of the discussed in vitro studies [19, 20, 23, 24] used very high lycopene concentrations up to 20 μM, not being physiologically relevant. When using lower concentrations between 0.5 and 2 μM, an unphysiologically long treatment of up to 24 h [21] was used. Thus, most of the effects shown in in vitro studies cannot be directly transferred to the in vivo situation.

 

## 4 In vivo studies

### 4.1 Animal studies

Bansal et al. [26] fed adult male Wistar rats with lycopene (1 mg/kg) dissolved in olive oil (1 mL/kg) for 31 days. Lycopene decreased levels of lipid peroxides and increased glutathione levels as well as glutathione peroxidase (GSH-Px) activity. Thus, intervention with lycopene in this study reduced oxidative stress in rats in contrast to other studies where it failed. In another experiment with female Wistar rats, lycopene was given for 2 wk at doses between 0.001 and 0.1 g/kg body weight (b.w.) per day. Activity of super oxid dismutase (SOD) was significantly induced at doses of 0.005 and 0.05 g/kg b.w. Activities of glutathione reductase and GSH-Px were only induced at 0.005 mg/kg b.w. per day. In contrast, activity of catalase (CAT) was not affected [27]. Gitenay et al. [28] investigated a rat model with mild oxidative stress induced by a diet low in vitamin E. Feeding (6 wk) none (control), 16% freeze-dried yellow tomato, 16% freeze-dried red tomato or 0.05% lycopene beadlets did not affect cholesterol concentration in plasma. Red tomato intervention decreased triacylglycerol levels compared to control, yellow tomato and lycopene beadlets. Thiobarbituric acid reactive substance levels in heart were lower after feeding red tomatoes and yellow tomatoes compared to control and beadlets. Thus, tomatoes had a higher potential than lycopene to affect oxidative stress-related parameters, possibly due to the synergy of all the phytochemicals in tomatoes.

Another animal experiment used hamsters and enriched their feed with tomato paste (t. p.) containing approx. 0.1% lycopene. Intervention (8 wk) was done with 3 or 9% t. p. containing 0.2% cholesterol. The authors observed reduced contents of total cholesterol (−14.3%) and LDL cholesterol (−11.3%) in serum due to feed with 9% t. p. HDL cholesterol was increased by 19.4% (3% t. p.) or by 28.8% (9% t. p.). In addition, MDA in plasma was reduced by 80.2% (3% t. p.) or by 89.3% (9% t. p.). Regarding the antioxidant enzymes, activities of CAT, SOD and GSH-Px were significantly increased after 8 wk feeding 9% t. p. [29].

Verghese et al. [30] fed (12 wk) a normal diet, a high cholesterol (5 g/kg) diet and a high cholesterol diet with different contents of lycopene (42.6/85.2/127.8 mg/kg) to male New Zealand white rabbits (five groups with five animals each). Lycopene significantly reduced serum cholesterol levels. The highest lycopene dose reduced serum cholesterol by 42.8% (increased fecal cholesterol and bile acid secretion). In addition, lycopene significantly increased HDL cholesterol levels. Lycopene also significantly reduced HMG-CoA reductase activity as well as acyl-CoA-cholesterol-acyltransferase activity. The highest dose of lycopene significantly reduced plaque area of the aorta by 64.3%. Thus, lycopene showed a cardioprotective effect in rabbits. In another experiment, 40 adult male New Zealand white rabbits in five groups got a standard diet, a high fat diet (5% lard, 1% cholesterol, 94% standard diet), a high fat diet plus 4 mg/kg of lycopene, a high fat diet plus 12 mg/kg of lycopene and a high fat diet plus 10 mg/kg of fluvastatin (one of the generally accepted drugs for treatment of coronary atherosclerosis). The intervention lasted 8 wk. The high fat diet led to increased levels of total cholesterol, total triacylglycerol, LDL cholesterol, IL-1. Lycopene was better than fluvastatin in counteracting the changes in these parameters. Lycopene and fluvastatin also markedly reduced the formation of atherosclerotic plaques in the aorta compared to the situation in rabbits on a high-fat diet alone [31]. In contrast, Frederiksen et al. [32] did not show any effect of an intervention (16 wk) with an extract of lycopene-rich tomatoes when investigating 65 male Watanabe heritable hyperlipidemic rabbits. They fed a control diet, a control diet supplemented with a mixture of plant oils or a control diet supplemented with the tomato extract (0.25 g tomato extract (containing 6% lycopene)/100 g:15 mg lycopene/100 g diet). The tomato extract had no effect on cholesterol and triacylglycerol levels in plasma, on cholesterol in lipoprotein fractions and on aortic atherosclerosis (cholesterol in tissue, microscopy). Oxidation of plasma lipids was also unaffected by the intake of the tomato extract.

Within the discussed animal experiments [26–32], intervention durations were between 2 and 16 wk, being also relevant for the human situation. Only the study with 2-wk intervention could be a bit too short to show more effects than the presented ones. Lycopene dosage might be a more critical parameter. The authors used lycopene dosages between 0.001 mg/kg b.w. [27] and 127.8 mg/kg diet [30]. As the animals partly had free access to the feed (e.g. [30]) and otherwise got a restricted amount (e.g. 100 g: [32]), the studies are not comparable. Experiments with a lycopene dose of approx. 10 mg/kg b.w. cannot be transferred to the human situation. In addition, it has to be considered that experiments with rats [26–28], hamsters [29] and rabbits [30–32] cannot be directly translated into the situation in the human organism.

### 4.2 Human intervention studies

In vitro studies as well as animal studies showed linkages between lycopene or tomato products and prevention of CVD. However, only well-designed human intervention studies are able to show the in vivo relevance of these beneficial effects of lycopene and tomato products.

Within a case-control study, 20 coronary heart disease patients were asked to eat 200 g cooked tomatoes (cooked with soybean oil) every day for 60 days. MDA levels were significantly reduced by supplementation with tomatoes, indicating a lower rate of lipid peroxidation. Supplementation with tomatoes also increased levels of antioxidant enzymes (SOD, glutathione reductase, GSH-Px) while lipid status parameters were not affected [33]. In a randomised, placebo-controlled, double-blind, crossover study 26 healthy

 

men and women were supplemented with placebo and verum for 26 days per period. Within the verum period, they ingested 5.7 mg lycopene (comprised in a tomato-based drink) per day. The tomato-based drink significantly reduced TNF-α production (−34.4%) in challenged whole blood. In contrast, deoxyribonucleic acid (DNA) damage and urinary 8-iso-$PGF_2\alpha$ concentration were not affected by tomato drink consumption [34]. Another randomised, placebo-controlled, double-blind study was recently published [35]. Supplementation of 126 healthy men, aged 22–57 years, with 6 or 15 mg lycopene (comprised in tomato oleoresin capsules) daily for 8 wk led to significantly increased lycopene contents in serum. Oxidative stress was reduced by lycopene uptake as was shown by decreased DNA damage as well as by increased SOD activity. Endothelial function was investigated using the reactive hyperemia peripheral arterial tonometry index, measuring the finger arterial pulse wave amplitude. Aliquots of 15 mg lycopene per day significantly increased the reactive hyperemia peripheral arterial tonometry index. This dose also significantly decreased hs-CRP content in serum, a marker of inflammatory status. Both lycopene doses significantly decreased the contents of the two adhesion proteins sICAM-1 and sVCAM-1 in plasma. Thus, supplementation with 15 mg lycopene per day over 8 wk was able to reduce oxidative stress as well as to improve endothelial function. This study specially focused on middle-aged Korean men; thus the results cannot be generalised to women. However, the results demonstrated antioxidative and anti-inflammatory effects of lycopene [35]. In contrast, in a recently published intervention with 31 non-smoking healthy postmenopausal women, intervention with 70 g tomato purée per day (46 mg lycopene per day) did not affect endothelial function. Although the concentration of lycopene in plasma significantly increased, flow-mediated dilation did not change during the intervention period [36]. Ried and Fakler [37] made a meta-analysis using human intervention trials between 1955 and September 2010, investigating the effect of lycopene on blood lipids or blood pressure. Their meta-analyses showed that lycopene is effective in reducing total cholesterol and LDL cholesterol in serum if taken in higher doses than 25 mg daily. A 10% reduction in LDL cholesterol is comparable to the effect of low doses of statin drugs and is clinically significant. LDL cholesterol-reducing properties have been associated with a decrease of cholesterol synthesis, an increase of LDL degradation and inhibition of HMG-CoA reductase. Only a small number of trials ($n = 4$) have investigated the effect of lycopene on blood pressure. They suggest for lycopene a lowering effect on systolic blood pressure, in particular in hypertensive subjects. Further studies are needed to confirm these results.

All human intervention studies presented [33–36] used healthy subjects. Thus, the authors of these studies investigated the possible primary preventive effect of lycopene comprised in tomatoes or tomato products. Some studies investigated only men [35] or women [36] while others used men and women as volunteers [33, 34]. This makes a comparison of the studies difficult. Duration of the intervention trials also varied between 7 days [36] and 8 wk [35]. In addition, the authors used lycopene dosages of 5.7 [34] up to 46.2 mg per day [36]. Thus, a direct comparison of the studies is not possible. The matrix of the intervention products (raw tomatoes, tomato-based drink, tomato oleoresin capsules, tomato purée) could be another factor having affected the results. The lycopene concentrations in plasma reached after intervention were often below or close to 1 μM, being thus much lower than the concentrations used in several in vitro studies. In vitro studies need to be better adapted to the in vivo situation to avoid, more often, discrepancies between them.

## 5 Patents and products

Recently, two products containing lycopene were patented, one from a company in Spain and another one from a company in the UK. The Spanish company submitted study data for a ''product for use in the prevention and treatment of CVDs, cancer and chronic inflammatory diseases'' [38]. Their product for oral consumption includes therapeutically effective amounts of oleic acid and lycopene (1–125 mg) together with suitable amounts of one or more other compounds (e.g. β-carotene, retinol, phytosterols). In context with CVD, they claimed antioxidant effects as well as regulation of inflammatory processes. The other patent [39] describes ''lycopene formulations for the treatment of atherosclerotic conditions''. The product is a lycopene–lactoprotein composition, containing a whey protein isolate and 7 mg lycopene per daily dose.

Another company from UK, producing a water-soluble tomato concentrate (not containing lycopene), applied for a health claim according to article 13(3) of regulation (EC) No. 1924/2006. With commission decision of 17 December 2009 a health claim on the effect of water-soluble tomato concentrate on platelet aggregation was authorised [40]. The company was authorised to use the following claim: ''*Water-Soluble Tomato Concentrate* (*WSTC*) *I and II helps maintain normal platelet aggregation, which contributes to healthy blood flow*''. Use of the claim was allowed only when information is given to the consumer that the beneficial effect is obtained with a daily consumption of 3 g WSTC I or 150 mg WSTC II in up to 250 mL of either fruit juices, flavoured drinks or yoghurt drinks. In contrast to this very specific functional claim allowed by the European Commission, there are products on the market with information (Internet) that Fruitflow® is a bioactive, patented extract from ripe tomatoes that helps the blood flow smoothly, which is important in maintaining a healthy heart and cardiovascular system. WSTC is an aqueous concentrate of t. p. that consists of soluble solids extracted from a commercially available t. p.

In addition, 21 requests, dealing with lycopene, for health claims according to Article 13(1) of regulation (EC) No.

 

1924/2006, submitted by the member states, were checked by the European Food Safety Authority (EFSA). EFSA agglomerated these 21 requests into one scientific opinion [41]. Regarding CVDs the claimed effects are ''*heart health*'' and ''*cardio-vascular health*'' with the general population as target population. In the context of the proposed wordings and clarifications provided by the member states, the EFSA panel assumed *maintenance of normal cardiac function* as claimed effect. On the basis of the data presented, the panel concluded that a cause and effect relationship has not been established between the consumption of lycopene and contribution to normal cardiac function.

## 6 Concluding remarks

Promising epidemiological studies, associating high levels of lycopene with low levels of oxidative stress (oxLDL, conjugated dienes) initiated numerous in vitro and in vivo investigations, looking for linkages between lycopene and risk for CVDs. However, already the epidemiological data are contradictory as in other studies no association was observed: between lycopene and the risk of acute myocardial infarction, between lycopene and markers of inflammation, between lycopene and endothelial dysfunction. In vitro experiments showed that lycopene significantly inhibited TNF-α-induced expression of ICAM-1 and VCAM-1 as well as activation of NF-κB. Pre-treatment of cells with lycopene significantly decreased MDA contents in $H_2O_2$-treated cells as well as rate of apoptosis by up-regulating p53 mRNA and caspase3 mRNA. Intracellular content of total cholesterol was reduced due to lycopene. Lycopene also reduced 7-ketocholesterol-induced ROS production and inhibited platelet aggregation as well as decreased rate of LDL oxidation. However, lycopene concentrations up to 20 μM and treatment periods of up 24 h make the in vitro studies difficult to transfer to the in vivo situation.

In Wistar rats, lycopene reduced concentration of lipid peroxides and increased activity of GSH-Px and SOD and content of glutathione. Tomatoes decreased contents of thiobarbituric acid reactive substances and triacylglycerols. A high cholesterol diet was fed to hamsters. Lycopene decreased total cholesterol, LDL cholesterol, MDA and increased HDL cholesterol as well as activity of CAT, SOD and GSH-Px. Treatment of New Zealand white rabbits with lycopene together with a high cholesterol diet significantly decreased cholesterol content in serum and plaque area in aorta while increasing content of HDL cholesterol in serum. Effects of lycopene were comparable to those of fluvastatin. In contrast, lycopene-rich tomatoes did not show any effect. The authors used lycopene dosages between 0.001 mg/kg b.w. and 127.8 mg/kg diet. As the animals also partly had free access to the feed and otherwise got a restricted amount, the studies are not comparable. Experiments with a lycopene dose of approx. 10 mg/kg b.w. cannot be transferred to the human situation. In addition, it has to be considered that experiments with rats, hamsters and rabbits cannot be directly translated into the situation in the human organism.

In human intervention studies, cooked tomatoes, a tomato-based drink as well as tomato oleoresin capsules increased activities of antioxidant enzymes (SOD, GSH-Px) and reduced MDA, TNF-α, DNA damage, hs-CRP. Significantly improved endothelial function was also measured in one study, while another trial showed endothelial function unaffected by consumption of t. p. Duration of the intervention trials varied between 7 days and 8 wk. In addition, the authors used lycopene dosages of 5.7 up to 46.2 mg per day. Thus, a direct comparison of the studies is not possible. However, all these investigations led to the development of different products containing lycopene. Some were already patented. One water-soluble tomato extract also got approval of a health claim while many others dealing with lycopene failed.

Thus, there is still a promising situation, giving hints for antioxidant as well as anti-inflammatory effects of lycopene. These mechanisms could be the background for cardioprotective effects of tomatoes and tomato products. However, there are a lot of investigations needed in the future to give reliable results to establish these CVD-preventive effects.

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