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Lycopene and its antioxidant role in the prevention of cardiovascular diseases ï a critical review

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Abstract

The present review is based mainly on papers published between 2000 and 2011 and gives information about the properties of the carotenoid lycopene in chemical and biological systems and its possible role in preventing cardiovascular diseases (CVD). The main aim of this report is to highlight its role as an antioxidant, also reported are bioactive properties that may influence the development of foam cells and protection against endothelial cell damage. The paper will also examine recent observations that lycopene may improve blood flow and reduce inflammatory responses. Lycopene possesses antioxidant properties *in vitro*, and some epidemiological studies have reported protective effects against the progression of CVD. The oxidation of human low density lipoproteins (LDL) is a fundamental mechanism in the initiation of atherosclerosis. A beneficial role of lycopene as antioxidant in the prevention of CVD is suggested but the data are still controversial. Lycopene is believed to be the most potent carotenoid antioxidant *in vitro*. Tissue culture experiments and animal studies support potential cardioprotective effects for lycopene and other carotenoids in the blood. Most studies showed beneficial effects of lycopene to individuals who are antioxidant-deficient like elderly patients, or humans exposed to higher levels of oxidative stress like smokers, diabetics, hemodialysis patients and acute myocardial infarction patients. By defining the right population and combining antioxidant potentials of lycopene with vitamins and other bioactive plant compounds, the beneficial role of lycopene in CVD can be clarified in future studies.

Keywords: atherosclerosis, isomerization, *in vitro*, *in vivo*, LDL oxidation

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Introduction

In the context of prevention of cardiovascular diseases (CVD), it is recommended to increase the consumption of fruits and vegetables, being good sources of various antioxidants, such as lycopene (Ruxton et al., 2006). There is increasing evidence to suggest that lycopene or processed tomatoes may lead to a reduction of intima-media thickness in vessel walls (Karppi et al., 2011). Recent studies indicate a role for tomato products in improving endothelial function and blood flow (Xaplanteris et al., 2012). In another study, a tomato product inhibited lipemia-induced postprandial oxidative and inflammatory responses (Burton-Freeman et al., 2012). Due to the high consumption of raw tomatoes and tomato-based products in the Western developed countries and developing countries, it is believed that tomatoes are the most important source of lycopene in North America with a contribution of approx. 80-85%, and that tomatoes and tomato products contribute to more than 30% of the total carotenoids content in the human diet (Omoni and Aluko, 2005; Rao et al., 2006). Lycopene intake in five European countries was assessed to be between 1.6 and 5.0 mg/d. Tomatoes contributed to the lycopene intake with 16% in The Netherlands up to 55% in Spain. When including also tomato products, the contribution to the lycopene intake in the five countries ranged between 56% and 97% (OôNeill et al., 2001). However, it should be noticed that the population used in this study was a group (ca. 80 subjects per country) in a determined area of the five participant countries. The lycopene levels in plasma are depending on the kind of diet and ranged between 0.4 µM in North and Central Europe up to 1.3 µM in South Italy (Jenab et al., 2005). Lycopene is generally the carotenoid showing the highest concentration in North American`s serum, but nevertheless the average adult serum concentrations are less than 0.13 µM (Erdman et al., 2009). Michaud et al. reported an average

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concentration of lycopene in plasma in the US-American Nursesô Health Study and the Health Professionals Follow-Up study of 0.80 ± 0.54 µM (Michaud et al., 1998).

The objective of this paper is to give a systematic overview on the antioxidant properties of the carotenoid lycopene with regard to the development of cardiovascular diseases and to describe the possible beneficial role of lycopene in humans as well as limitations.

Methods

In the systematic review, Medline and Chemical Abstracts Service (CAS) database searches using Pubmed, Scifinder and Scopus have been performed, using all combinations of antioxidant(s), lycopene and cardiovascular/atherosclerosis. The database searches were conducted in August 2011. Some later published additional articles were included within the process of revision of the manuscript.

The following inclusion criteria have been used in the systematic review:

- Studies in humans only.
- Studies published from 2000 onwards.
- Only studies reporting on original data. Review articles, editorials, textbook chapters, etc. have been used only to identify articles with original data.
- Only articles with case-control, cohort or randomized controlled trial (RCT) study design.
- Studies of lycopene, its isomers and its possible metabolites only; other antioxidant lipophilic substances like other carotenoids, tocopherols, selenium, lipoic acid, ubiquinone and synthetically drugs with antioxidant properties have not been included.

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- Studies on the effects of antioxidants as primary prevention against cardiovascular diseases. Effects of antioxidants to prevent recurrences or disease progression (secondary prevention) have only been summarised, and studies performed in subgroups such as diabetic subjects have not been reviewed.
- Articles on the relationship between consumption of food compounds and cardiovascular diseases without data on contents of antioxidant substances have not been included.

Within the systematic review, 169 (33) papers were retrieved in Pubmed, 263 (79) in Scifinder and 233 (98) in Scopus. The numbers in brackets are review papers thereof. Many of the retrieved papers were included in this manuscript.

Additional articles have been retrieved by scrutinizing reference lists of published articles considered as relevant within the systematic review. These additional articles present also data from *in vitro* studies as well as from cell culture experiments, in contrast to the inclusion criteria for the systematic review. Papers published before 2000 were also included as additional articles as they give important details with relevance for the review presented here.

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General properties of lycopene

Lycopene is a natural pigment, mainly present in tomato, which belongs to the carotenoid family and more precisely to the carotenes subgroup since it is exclusively composed of carbon and hydrogen atoms ($C_{40}H_{56}$) (Britton et al., 2004). Like the majority of carotenoids, lycopene is a tetraterpene. Among carotenes, lycopene is characterized by a symmetric and acyclic structure containing 11 linearly arranged conjugated double bonds. Lycopene can be considered as the ñprototypeò of most carotenoids, since their structures can be related to lycopeneôs through structural modifications. In the nomenclature of the International Union of Pure and Applied Chemistry (IUPAC) for carotenoids (IUPAC, 1971, IUPAC, 1975), lycopene is called ɣ,ɣ-carotene.

In nature, lycopene is mostly present under its *all-E*- (or *all-trans*-) form (Figure 1), but some double bonds can be isomerized into *Z*- (or *cis*-) form, thus giving *Z*- (or *cis*-) lycopene isomers (Figure 1). Theoretically, each one of the 11 carbon-carbon double bonds can undergo isomerization to produce an array of mono- or poly-*Z*-isomers of lycopene, all together 2^{11}=2048 isomers are possible. But because of steric hindrance, only some ethylenic groups can be isomerized from *E* to *Z* form (Weedon and Moss, 1995). Indeed about 72 lycopene *Z*-isomers are structurally favorable and only some have been observed (Figure 1). For instance, one example of *Z*-lycopene isomer in nature is (*tetra-Z*)-lycopene ((*7Z,9Z,7'Z,9'Z*)-lycopene, Figure 1) found in the tangerine tomato variety (Englert et al., 1979), also called prolycopene.

Conversion of (*all-E*)-form to (*Z*)-isomers of lycopene can occur in presence of light, exposure to heat or by specific (bio) chemical reactions.

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Because of its conjugated structure, (*all-E*)-lycopene is a quite unstable molecule when isolated. It is highly susceptible to oxidation, and also to exposure to light, high temperatures and extreme pH. However, in its natural matrix, i.e. tomato, lycopene was shown to be rather stable, maybe through protection by the matrix itself since lycopene is located inside the cells thus probably protected by the cell membrane. Degradation compounds of lycopene, usually found in food matrix and *in vitro* oxidation models, are issued from oxidation and/or cleavage reactions (Caris-Veyrat et al., 2003). Lycopene epoxides were observed in heated tomato purée (Chanforan et al., 2012) and can be formed *in vitro* by chemical reaction with *meta*-chloro-perbenzoic acid. But lycopene epoxides are unstable molecules and usually rearrange in acidic medium to form cleavage compounds called apo-lycopenoids, with a ketone or an aldehyde ending function. Apo-lycopenoids with aldehyde ending functions, i.e. apo-lycopenals, have been detected in heated tomato products (Chanforan et al., 2012; Kopec et al., 2010) and also in plasma of volunteers who had consumed tomato food products (Kopec et al., 2010). Apo-lycopenoids could be natural metabolites of lycopene, but this has not been fully proven yet. Like other carotenoid oxidation products, they could have biological activities either similar and/or improved or different from those of lycopene (Carail and Caris-Veyrat, 2006; Khachik, Beecher, and Smith, 1995; Wang, 2004) concerning antioxidant or cell-signalling activities (Reynaud et al., 2011). For instance, in an *in vitro* model mimicking oxidative stress of dietary origin, we were able to show that long-chain apo-lycopenoids display better antioxidant properties than lycopene (Müller et al., 2012) and that the chain length and the ending function of the apo-lycopenoids can modulate their antioxidant activity and mechanisms (Goupy et al., 2011). Diapo-lycopenoids were shown to exert a higher cell-signalling effect than lycopene in the ARE transcription system (Linnewiel et

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al., 2009) and apo-10'-lycopenoic acid was proven to have an impact on adipose tissue biology via the retinoic acid receptors (Gouranton et al., 2011).

Theories to the progression of CVD

The oxidation of human LDL is a fundamental mechanism in the initiation of atherosclerosis. The presence of this modified lipoprotein in the sub-intimal space of an artery is recognized by scavenger receptors, CD36 and SRA-1 expressed by macrophages. The oxidized LDLs are rapidly removed by macrophages, and if the LDL particles are rich in lipids and cholesterol, then the formation of ófoam cellsô is more likely to occur. Foam cells are one of the more easily recognized cells present in fatty streaks, the primary lesion identified in atherosclerosis. The altered characteristics of the macrophage means that cholesterol is retained within the arterial cell wall, and foam cells secrete growth factors that encourage the growth of smooth muscle cells in the medial layer of the artery and they also secrete metalloproteinases that may destabilize the plaque, tissue factors that encourages platelet aggregation upon disruption of the plaque (Kruth et al., 2002).

There are several theories that account for the initiation of atherosclerosis, including the response to injury (Nofer et al., 2010), the oxidative modification (Jessup et al., 2004) and the inflammatory model (Libby et al., 2002; Paoletti et al., 2004; Shah, 1999).

One common factor with all of the three described theories is the presence of oxidized LDL. Regarding the structure, LDL particles comprise of a single copy of apolipoprotein B100 (apoB100), phospholipids, cholesterol esters, free cholesterol, triglycerides and lipid soluble antioxidants such as tocopherols, ɓ-carotene and lycopene. The apoB100 and phospholipids are

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distributed towards the surface to aid stabilization of the hydrophobic core (Segrest et al., 2001). The composition of the core may vary from one particle to another and from individual to individual. This means that some individuals are present with a distribution of LDL particles that are smaller and more-dense, and these particular individuals may be at greater risk of developing atherosclerosis (McNamara et al., 1996; Rizzo and Berneis, 2007).

Mechanisms of LDL oxidation

There is much debate as to the nature of the oxidants that can initiate oxidative modifications to LDL particles. The modification of apoB100 is responsible for the uptake of modified LDL. Certain products from lipoperoxidation such as nonenal can result in structural modifications of the protein. This section will only confine itself to three oxidizing agents implicated in oxidation of LDL: myeloperoxidase, peroxynitrite and metal ions.

Myeloperoxidase

The sources of myeloperoxidase (MPO) in the vascular wall are primarily derived from macrophages and monocytes. The enzyme requires hydrogen peroxide as its substrate. This can be generated through the activity of NADPH oxidase, present on endothelial cells or on monocytes. NADPH oxidase generates superoxide, which can be dismutated through the action of superoxide dismutase or through other interactions in the sub-intimal space to form hydrogen peroxide. Myeloperoxidase converts the hydrogen peroxide to hypochlorous acid. Hypochlorous acid is a potent oxidant that can rapidly oxidize proteins and induce lipoperoxidation in LDL particles (Carr et al., 2000). Other reactions are worth considering in regard to myeloperoxidase as it can also react with other halides such as bromine to produce hypobromous acid, or the hypochlorite may react with nitrite or other nitrogen species to produce nitryl chloride

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(Armstrong, 2001). It was also demonstrated that myeloperoxidase can oxidize thiocyanate to cyanate, which through the process of carbamylation can modify structure and function of proteins (Basnakian et al., 2010). The chlorination and nitration of tyrosine residues present in apoB100 may also occur through the action of myeloperoxidase. Both 3-chlorotyrosine and 3-nitrotyrosine have been used as biomarkers of MPO-catalyzed oxidation.

Several previous studies have examined the role of myeloperoxidase in initiating lipoperoxidation in human LDL particles. These studies indicated that protein is the main target for myeloperoxidase when the MPO:LDL molar ratio is less than 200:1. When MPO exceeds this ratio, only then is there prevalence towards lipoperoxidation (Malle et al., 2006).

In vitro studies indicated that pure lycopene is degraded by the activity of myeloperoxidase. There is a depletion of (*all-E*)-lycopene, along with the formation of many oxidation products including (*Z*)-isomers, epoxides and shorter chain derivatives of lycopene including lycopenals and lycopenoids (Chew et al., 2012; Pennathur et al., 2010). When isolated human LDL is challenged by MPO, there is an oxidation of apoB100 followed by lipoperoxidation. If radicals from MPO reach the centre of the LDL particles, then a depletion of lycopene would be expected to occur. In a recent study, no alteration in lycopene concentration, but oxidation of apoB100 and the formation of 7-ketocholesterol were observed. This would indicate that the surface of the LDL particle is more prone to modification following MPO activity and that lycopene has only a very minor if any role as an antioxidant (Chew et al., 2012).

Peroxynitrite

The chemical generation of peroxynitrite ($^{-}$ONOO) is dependent upon the generation of nitrous oxide (NO) and superoxide. Endothelial cells are able to produce superoxide through several

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mechanisms including the action of NADPH oxidase (NOX). And nitric oxide is formed through the action of NO synthase (eNOS). Superoxide can be produced by xanthine oxidase, binding to endothelial cell surfaces, or through the activity of NOX1, 2 and 4. Both these radicals combine to form peroxynitrite.

$NO^{Å}$ + $O_2^{Å}$ Ÿ $ONOO^-$

Peroxynitrite can interact with LDL particles in a number of ways. The first mode of action is the initiation of lipoperoxidation. If the sub-intimal space has a lower pH, a peroxynitrous acid is formed that may decompose to form NO and a hydroxyl radical which can initiate lipoperoxidation through proton abstraction from polyunsaturated fatty acids. Alternatively, peroxynitrite could interact with apoB100 which may lead to the nitration of L-tyrosine or phenylalanine.

In vitro studies indicate that lycopene can scavenge nitric oxide and peroxynitrite and that isolated human LDL is depleted of lycopene following challenge with agents such as sin-1 (Graham et al., 2010; Muzandu et al., 2006). Cigarette smokers are associated with lower carotene and xanthophyll concentrations in plasma (Al-Delaimy et al., 2005; Gabriel et al., 2006). This may be due to peroxynitrite, generated in the gaseous phase of cigarette smoke, crossing the lung alveolus and interacting with LDL particles. This would certainly account for the increase of circulating oxidized LDL observed in smokers (Kassi et al., 2009), and may contribute to a decrease in the circulating carotenoid concentrations.

Many nitrated polyunsaturated lipids along with tocopherols and ß-carotene have been isolated *in vitro* (Morton et al., 2002; Lowe et al., 2009). However, at this time there are no reports of nitrated lycopene being detected in human plasma.

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Metal ions

Much of the early work investigating the oxidation of human LDL was performed using copper ions. The oxidation of the LDL was monitored using TBARS, a colorimetric assay, and the oxidation of the LDL particle using agarose electrophoresis. The oxidation of the isolated LDL fraction was characterized by a lag-time which was associated with the consumption of antioxidants. Esterbauer (Esterbauer et al., 1992) indicated that tocopherol was the first component to be consumed in this process as these molecules are located toward the periphery of the LDL particle. Lycopene was one of the final antioxidants to be consumed. Following the lag-time, a propagation phase occurred leading to the oxidation of apoB100. These oxidation mechanisms assisted the early *in vivo* studies on the identification of antioxidants which could reduce the lag-time. However, there have been varied reports concerning lycopene when this method was adopted (Ahuja et al., 2006; Silaste et al., 2007; Visioli et al., 2003; Wright et al., 2002). One explanation is that the free metal acts on preformed peroxides present in the LDL particle (Thomas et al., 1994; Frei and Gaziano, 1993). In some studies that employed harsh isolation and purification treatments of LDL, then the quality of isolated LDL was being assessed rather than antioxidant activity. Usually, metal ions are normally tightly bound to proteins in the body to prevent Fenton type reactions from occurring. Some studies have indicated that free metal ions have been located in ruptured plaques or more advanced stages of atherosclerosis (Swain and Gutteridge, 1995). Metal ions may play a role in more advanced cases rather than in initiating atherosclerosis.

The question remains, does lycopene have any antioxidant properties that may protect against LDL oxidation? The first problem is the location of the lycopene or its isomers, which are

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situated toward the centre of the LDL particle. This positioning is important as radicals need to penetrate the LDL particle for lycopene to become an effective antioxidant. Several studies indicate that the mean number of lycopene molecules per LDL particle is restrictive to being an effective antioxidant. The current estimate is that there is only one lycopene molecule per LDL particle (Milde et al., 2007; Romanchik et al., 1995). However, LDL particles are heterogeneous. Thus, very little lycopene is present in the smaller more dense LDL fraction, but the majority of lycopene is associated with the mid-density LDL particles (Lowe et al., 1999). This would mean that in some LDL particles there will be more than one molecule of lycopene, and it may have an antioxidant role in those particles.

Effect on macrophages

Oxidized LDL particles are cleared by macrophages in the sub-intimal space of the artery. This is done through scavenger receptors such as SRA-1 or CD36 (Vainio and Ikonen, 2003). The oxidized LDL particles are then processed, releasing cholesterol, lipids and lycopene. Many studies have indicated that lycopene or metabolites of lycopene may have bioactive properties (Reynaud et al., 2011; Müller et al., 2012; Ford et al., 2011) and may influence the physiology of cellular function by promoting or inhibiting signalling pathways. One such study (Napolitano et al., 2007) indicated that lycopene may decrease lipid synthesis in the macrophages along with decreased scavenger receptor expression. These two observations suggest that lycopene may play a role in inhibiting the formation of a foam cell in the arterial space. However, in this study it was also observed that the synthesis of IL-10, an anti-inflammatory marker, was inhibited in lycopene supplemented macrophages exposed to oxidized LDL. This would also indicate that lycopene could also be a pro-inflammatory agent.

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Lycopene can interact with more lipid soluble radicals, and may help prevent LDL oxidation. Lycopene is present in low numbers per LDL particle but for mid density LDL particles there may be more than just one lycopene molecule per particle. Lycopene may also act synergistically with surrounding carotenes or xanthophylls or tocopherols to prevent LDL oxidation. The conformation of lycopene is also not entirely understood, and the presence of an increased ratio of (*Z*)-isomers to (*all-E*)-lycopene may reflect the degree of free radical challenge to the LDL particle (Erdman et al., 2009; Mortensen et al., 2001; Woodall et al., 1997).

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Lycopene as cardiovascular relevant antioxidant *in vitro*

1) Chemo-analytical studies

Lycopene is believed to be the most potent carotenoid antioxidant *in vitro* (Di Mascio et al., 1989; Miller et al., 1996; Woodall et al., 1997; Stahl and Sies, 2003; Müller et al., 2011b). Lycopene as a carotenoid can react with types of reactive oxygen species (ROS) in three different mechanisms: I) by electron-transfer (ET), II) by hydrogen atom transfer (HAT) or III) by adduct formation (Kong et al., 2010; Krinsky and Yeum, 2003). Which type of reaction between the carotenoid and the ROS is preferred depends on the molecular structure of the carotenoid and the kind of ROS.

Lycopene is able to deactivate **singlet oxygen** mainly by physical quenching. Only 0.05% of carotenoid activity is chemical quenching (Wagner and Elmadfa, 2003). In quenching singlet oxygen ($^1O_2$) in homogenous solution, lycopene was twice potent compared to ß-carotene and 10-times more active than Ŭ-tocopherol (Di Mascio et al., 1989; Sundquist et al., 1994). Incorporated in human serum albumin as well as in Dipalmitoylphosphatidylcholin (DPPC) membranes, lycopene and ß-carotene displayed similar activity against $^1O_2$ (Yamaguchi et al., 1999; Cantrell et al., 2003). Controversial results were observed in autoxidation experiments of liposomal membranes formed from cholesterol and dilinoleoylphosphatidylcholine. Similar to ß-carotene, lycopene was incorporated in the inner hydrophobic part of the membranes and the LDL particles due to its high lipophilicity. The X-ray experiments showed that both carotenoids disordered model membranes and stimulated lipid peroxidation of the included unsaturated fatty acids. In contrast, xanthophylls, which are located in membranes like rivets and their polar end

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groups were oriented to the water phase, and especially astaxanthin decreased the levels of lipid hydroperoxides significantly (McNulty et al., 2008).

In contrast to ß-carotene which adds **superoxide** radicals ($O_2^{\dot{A}}$), lycopene reacts with $O_2^{\dot{A}}$ by electron-transfer (Conn et al., 1992). However, computational studies of Galano et al. (2010) showed that both carotenes should be less active in quenching $O_2^{\dot{A}}$ than xanthophylls, especially carbonyl-containing ones like canthaxanthin and astaxanthin (Galano et al., 2010).

Besides singlet oxygen and superoxide, **hydrogen peroxide** (H_2O_2) plays an important role as non-radical oxidant in the human vascular system. Most of the releasing H_2O_2 is reduced by erythrocyte-standing catalases. Aside, exogenous antioxidants in the blood stream can be helpful to support the protective action of these enzymes to prevent damages of blood lipids caused by H_2O_2. Lu et al. (1995) showed that lycopene reacts under acidic conditions with H_2O_2, forming lycopene-1,2-epoxide and 2,6-cyclolycopene-1,5-epoxide. In human serum and milk, 2,6-cyclolycopene-1,5-epoxide is present, as was firstly described by Khachik et al. (1997) and could be a possible metabolite of the reaction of lycopene with H_2O_2.

Chain-breaking antioxidants are able to inhibit the propagation phase of lipid peroxidation by scavenging **peroxyl radicals** amongst others. To analyze the ability of compounds to act as a chain-breaking antioxidant *in vitro*, peroxyl radicals were most often generated by thermal degradation of diazo compounds such as 2,2'-azo-bis(2,4-dimethylvaleronitrile) (AMVN), 2,2'-azo-bis(isobutyronitrile) (AIBN) and 2,2'-azo-bis(2-methylamidinopropane) (AAPH). The activity of plasma antioxidants (e.g. lycopene) to deactivate peroxyl radicals depends on the location of the peroxyl radicals and the antioxidants and therefore on their polarity. In a plasma model, lycopene was the strongest carotenoid against peroxyl radicals formed by thermal

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degradation of the more hydrophilic azo-compound AAPH, however less antioxidant than Ŭ-tocopherol and hydrophilic antioxidants. In contrast, against an attack of peroxyl radicals, initiated by the apolar MeO-AMVN, carotenoids action was comparable to that of Ŭ-tocopherol (Yeum et al., 2003). Our own studies using AAPH in a homogenous model system showed lycopene being approx. 10-times more active than Ŭ-tocopherol but less active than the more polar xanthophylls, which possibly showed higher activity than lycopene or ß-carotene due to a better availability by polar AAPH radicals (Müller et al., 2011b). Especially the carbonyl-containing xanthophylls with their highly unsaturated polyene chain were more effective in scavenging peroxyl radicals formed from AAPH, which supports the theoretical investigations of Guo and Hu (2010). But not only in homogenous solution, also in inhibiting oxidation of multilamellar liposomes by AMVN radicals, measured by the formation of TBARS, lycopene was the most antioxidant carotenoid; twice as active as Ŭ-carotene and 3-times more active than ß-carotene (Stahl et al., 1998). However, by using egg-yolk phosphatidylcholine based liposomes, lycopene was destroyed much faster than xanthophylls and Ŭ-tocopherol by using AAPH and AMVN as radical generators, but was the lowest antioxidant due to its orientation in the inner core of the micelles (Woodall et al., 1997; Woodall et al., 1995).

To assess the antioxidant activity of hydrophilic as well as that of lipophilic compounds, such as lycopene, various high-throughput methods were developed using different types of **synthetic oxidants** such as ABTS and DPPH. Using the synthetic 2,2'-azino-bis(3-ethylbenzothiazolin-6-sulfonic acid) radical cation ($ABTS^{•+}$) several times, lycopene was observed to be the most antioxidant carotenoid and 2- to 4-times more active than Ŭ-tocopherol (Miller et al., 1996; Müller et al., 2011b; Özyürek et al., 2008). The DPPH assay is a very popular method to analyze

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the antioxidant activity, especially of alcoholic-soluble compounds such as polyphenols, vitamin C and extracts and oils of fruits, vegetables and spices. In contrast, the activity of lycopene and carotenoids in general in scavenging the synthetic RNS (Reactive Nitrogen Species) 2,2-diphenyl-1-picrylhydrazyl radical ($DPPH^{Å}$) is negligible till not present. In our own studies, carotenes and xanthophylls did not react with DPPH. Only Ŭ-tocopherol, which was used as reference, showed activity (Müller et al., 2011b). The studies of Liu et al. (2008) showed that lycopene did not act in a concentration-depended relation with DPPH. With increasing concentrations of the carotenoid, the DPPH scavenging rate decreased. Similar results were obtained for ß-carotene (Liu et al., 2008).

Transitions metals such as $Fe^{2+/3+}$ and $Cu^{+/2+}$ play an important role in the initiation of lipid peroxidation and the progression of lipid peroxidation associated diseases. Iron could be released in the gastro-intestinal tract (GIT) from heme-containing proteins, especially in a diet rich in meat, and can oxidize lipids, which could be absorbed thereafter (Halliwell et al., 2000). The ferric reducing antioxidant power (FRAP) assay is a fast-acting method to analyze the activity of antioxidants to reduce ferric ions (Benzie and Strain, 1996). In our recent studies, we showed that lycopene is able to reduce ferric ions, which were incorporated in an organic complex, with similar activity like the xanthophylls lutein and zeaxanthin and twice as active as the antioxidant vitamins Ŭ-tocopherol and ascorbic acid. In contrast, in several studies the ionone ring containing carotenes (Ŭ- and ß-carotene) did not show FRAP activity (Müller et al., 2011b; Özyürek et al., 2008; Pulido et al., 2000; Müller and Böhm, 2011). Additionally, similar relationships between lycopene, Ŭ-tocopherol and ascorbic acid were observed in the cupric ion reducing antioxidant capacity (CUPRAC) assay, which measures the activity of compounds to reduce Cu^{2+}, based on

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principles similar to the FRAP assay (Özyürek et al., 2008). In a postprandial model of oxidative stress, physiological concentrations of lycopene inhibited the lipid peroxidation activity of metmyoglobin, a hemeprotein, against linoleic acid under mildly acidic conditions (pH 5.6) (Goupy et al., 2011; Müller et al., 2011c).

Lycopene can also function as a potent scavenger of **hypochlorous acid** (HOCl). HOCl is generated enzymatically by myeloperoxidase (MPO), a neutrophil-derived heme peroxidase, which uses H_2O_2 to catalyze a two-electron oxidation of chloride. HOCl is implicated as a contributing factor in a number of pathological conditions including inflammatory diseases, and atherosclerosis (Tsimikas and Miller, 2011; Hazen and Heinecke, 1997). In lipids, the major sites of attack by HOCl are the double bonds of unsaturated fatty acids or cholesterol, leading to peroxidation or chlorohydrins formation (Winterbourn and Kettle, 2000; Zhang et al., 2002). In addition, HOCl can react with other compounds to form other ROS such as $^{•}OH$ and $O_2^{•-}$ (Candeias et al., 1993). These ROS can cause further cellular damages. Recently, Pennathur et al. (2010) could show in homogeneous solution, that lycopene scavenges HOCl in a dose-dependent manner. By using LC-MS they showed that multiple molecules of HOCl were consumed per molecule of lycopene and a wide range of possible lycopene degradation products were evaluated, such as apo-lycopenals and carotendials (Pennathur et al., 2010).

Lycopene reacts also most effectively with **nitrogen dioxide radical** ($NO_2^{•}$) compared to other carotenoids. The order of reactivity was found to be: lycopene > ß-carotene > ß-cryptoxanthin > lutein/zeaxanthin > canthaxanthin = astaxanthin (Mortensen et al., 1997). Consequently, the sequence of reactivity was closely related to the reaction with the synthetic RNS-dye $ABTS^{•+}$

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(Miller et al., 1996; Müller et al., 2011b) due to the fact, that the reaction of both nitrogen-based radicals with carotenoids is based on electron-transfer.

But lycopene is not only described as a scavenger of ROS, RNS and ROCl, lycopene is also able to deactivate **sulfur-based radicals** on a higher rate than diet-relevant xanthophylls. Experiments with *in vivo* relevant glutathione-thiyl ($G\text{-}RS^{Å}$) and thiyl-sulfonyl ($RSOO^{Å}$), which can be formed by reaction of thiyl with molecular oxygen, showed that lycopene reacts 2.5-times faster than lutein, zeaxanthin, canthaxanthin and astaxanthin by ET-mechanism or adduct formation (Mortensen et al., 1997) due to its larger system of conjugated double bonds.

Carotenoids are susceptible to isomerization and oxidation. Heat, light and acids can promote isomerization of (*all-E*)-carotenoids to their (*Z*)-forms, resulting in a loss of color (Rodriguez-Amaya, 2001; Shi and Le Maguer, 2000). Non-enzymatic oxidative degradation is the main cause of extensive loss of carotenoids. It depends on the availability of oxygen and could be stimulated by light, metal ions and lipid hydroperoxides (Henry et al., 1998; Boon et al., 2009). Furthermore, oxidizing enzymes can lead to carotenoid oxidation and degradation. Undesirable degradation of lycopene not only affects the sensory quality of the final products, but also the health benefits of tomato-based foods for the human body (Shi and Le Maguer, 2000). In model systems (exposure to cigarette smoke), lycopene was the carotenoid most susceptible to smoke-induced oxidation. The degradation of lycopene was faster than that of ϐ-carotene, lutein and zeaxanthin (Hurst et al., 2004). The contribution of (*Z*)-isomers of lycopene in processed tomato-based products should not be underestimated. Whereas the (*all-E*)-form is the main isomer of lycopene in raw tomatoes (up to 96% of total lycopene) the proportion of (*Z*)-isomer was 4% to 27% in various tomato-based products such as spaghetti sauce (Schierle et al., 1997).

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Furthermore, (*Z*)-isomers of lycopene contribute to over 50% to total lycopene content in human plasma, with (*5Z*)-, (*9Z*)-, (*13Z*)- and (*15Z*)-lycopene as the predominant mono-(*Z*)-forms (Schierle et al., 1997). (*5Z*)-Lycopene is the predominant (*Z*)-isomer of lycopene in human plasma with a contribution of approx. one third to total lycopene content (Fröhlich et al., 2006).

In simple antioxidant activity assays, the most important lycopene (*Z*)-isomers displayed the same oxidant reducing activities as the (*all-E*)-form. (*5Z*)-, (*9Z*)-, (*13Z*)-lycopene as well as the tetra-*Z*-isomer found in Tangerine tomato varieties were similar antioxidant in reducing ferric ions in the FRAP assay and in bleaching the $ABTS^{\bullet+}$ in the TEAC assay (Müller et al., 2011c).

In a postprandial model of oxidative stress, the (*5Z*)-isomer of lycopene was more active than the *(all-E)*-form, and 50% more active than β-carotene and 3-times more active than α-tocopherol (Müller et al., 2011c).

In the more complex studies of Palozza et al. (2010), the activity to inhibit oxidative stress and apoptosis of THP-1 cells induced by 7-ketocholesterol of the (*5Z*)-isomer of lycopene was not significantly different to the activity shown by the (*all-E*)-isomer.

2) *In vitro* cell studies

Recently, Tang *et al.* reported, that lycopene in concentrations of 0.2-20 µM was able to protect ECV304 endothelial cells against oxidative attacks by H_2O_2, measured by reduced MDA levels compared to a control group (Tang et al., 2009). TNFα-induced intercellular adhesion molecule-1 (ICAM-1) expression in HUVECs was inhibited by lycopene in human umbilical endothelial cells (HUVECs), whereas cyclooxygenase-2 (COX-2) and platelet-endothelial cell adhesion molecule (PECAM-1) expression were not affected (Hung et al., 2008). In a functional study, lycopene dose-dependently attenuated monocyte adhesion to endothelial monolayers but not that

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adhesion to the extracellular matrix. Additionally, lycopene down-regulated the expressions of p53 and caspase-3 mRNA induced by H_2O_2 on a similar level as probucol, which is known as an effective antioxidant drug against CVD (Yamashita and Matsuzawa, 2009). These findings suggest that lycopene may act as an anti-atherogenic agent by a mechanism involving, at least in part, an antioxidant mechanism (Palozza et al., 2010).

Experiments with the human macrophage cell line THP-1 showed an effective inhibition of oxidative stress and apoptosis induced by 7-ketocholesterol (7-KC), an oxysterol with pathophysiological relevance in atherogenesis (Palozza et al., 2010). Physiologically relevant doses (0.5-2 µM) of (*all-E*)-lycopene and its (*5Z*)-isomer significantly reduced the increase in ROS production and in 8-hydroxydeoxyguanosine (8-OHdG) formation induced by the oxysterol in a dose-dependent manner. Summarized, lycopene was more effective than ϐ-carotene in counteracting the dangerous effects of 7-KC in human macrophages. The authors suggested that lycopene is a potential antiatherogenic agent to prevent oxidative stress and apoptosis of human macrophages (Palozza et al., 2010). Furthermore, lycopene in the above mentioned concentrations reduced the intracellular content of total cholesterol in the THP-1 macrophages by reduction of the expression of 3-hydroxy-3-methylglutaryl-coenzym A (HMG-CoA) reductase (Palozza et al., 2011). Due to hypercholesterolemia as one risk factor for atherosclerosis, this implies a potential role of lycopene in decreasing foam cell formation and therefore in the risk reduction of CVD.

Lycopene concentration-dependently (2-12 µM) inhibited platelet aggregation in human platelets stimulated by agonists. This phosphorylation was markedly inhibited by lycopene in phosphorus-32-labeled platelets. These results indicated that the antiplatelet activity of lycopene may involve

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the inhibition of the activation of phospholipase C, and lycopene also activated the formations of cyclic GMP/nitrate in human platelets, resulting in the inhibition of platelet aggregation. The results may imply that tomato-based foods are especially beneficial in the prevention of platelet aggregation and thrombosis (Hsiao et al., 2005).

3) Epidemiological studies

Kim *et al.* observed an inverse relationship between circulating lycopene, by measurements of lycopene content in serum, and arterial stiffness (measured by brachial-ankle pulse wave velocity, baPWV) in 264 healthy women (31-76 y). One hypothesis on the development of cardiovascular diseases is based on the oxidation of LDL, with antioxidants possibly preventing the formation of oxidized LDL. In this recent human intervention study, lycopene uptake was inversely correlated with a reduced oxidative modification of LDL (Kim et al., 2010).

Several epidemiological studies have suggested that high concentrations of carotenoids in plasma may slow the development of early atherosclerosis. Karppi et al. (2011) examined the effect of carotenoids on early stage of atherosclerosis in the population of Eastern Finland. The association between plasma carotenoid concentrations and intima-media thickness of the common carotid artery (CCA-IMT) was investigated in 1212 elderly men (aged 61-80 years). B-mode ultrasound was used to detect early signs of carotid atherosclerosis, and plasma concentrations of carotenoids were measured by HPLC. After adjustment for age, examination year, body mass index, smoking, alcohol intake, years of education, symptomatic coronary heart disease (CHD) or CHD history, diabetes, LDL cholesterol, medications and season, the concentrations of ß-cryptoxanthin, Ŭ-carotene and lycopene in plasma decreased linearly with increasing CCA-IMT(Karppi et al., 2011).

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In contrast, in the Physiciansô Health Study, investigating 499 cases of CVD and an equal number of men free of CVD, not any association of higher concentrations of lycopene in plasma of old men (69.7 ± 8.1 y) with the risk of CVD was shown (Sesso et al., 2005). Within the Kuopio Ischaemic Heart Disease Risk Factor (KIHD) cohort, 1031 Eastern Finnish men, aged 46-65 y, were investigated. Low levels of lycopene in serum were not significantly related to increased risk of CVD mortality (Karppi et al., 2012a). Within the same study, lycopene was also not related to the risk of sudden cardiac death in men (Karppi et al., 2013).

Looking only for the risk of stroke, after adjustment for age, examination year, BMI, systolic blood pressure, smoking, serum LDL cholesterol, diabetes and history of stroke, the KIHD study showed for men in the highest quartile of serum lycopene concentrations 59% and 55% lower risks of ischemic stroke and any stroke (Karppi et al., 2012b).

4) *In vivo* studies

As observed in chemical models, lycopene was able in an *in vivo* human intervention study to protect human lymphocytes against $^1O_2$ by energy transfer (Böhm et al., 2001). Similar results were observed in the protection against NO_2 radicals. However, the reaction was based on electron transfer (Böhm et al., 2001).

In another *in vivo* study, thrombus formation was induced by irradiation of mesenteric venules in mice pretreated with fluorescein sodium. Lycopene, in concentrations of 5, 10, and 20 mg per kg, significantly prolonged the latency period for the induction of platelet-plug formation in mesenteric venules (Hsiao et al., 2005).

In contrast to some epidemiological studies, none of the systemic markers such as inflammatory markers, markers of insulin resistance and sensitivity changed significantly in the plasma after a

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dietary intervention in the study of Thiess et al. (2012). After a 4-week run-in period with a low-tomato diet, a moderately overweighed group of 225 volunteers (94 men and 131 women) aged 40-65 years was randomly assigned into 1 of 3 dietary intervention groups and asked to consume a control diet low in tomato-based food, a high-tomato-based diet, or a control diet supplemented with lycopene capsules (10 mg/d) for 12 weeks. During the intervention, blood pressure, weight, and arterial stiffness were measured. Dietary intake was also determined. The study resulted in absent changes of lipids concentrations and arterial stiffness, though carotenoid profile changed and total concentrations increased (Thies et al., 2012). These data indicate that a relatively high daily consumption of tomato-based products (equivalent to 32-50 mg lycopene/d) or lycopene supplements (10 mg/d) is ineffective at reducing conventional CVD risk markers in short-term studies.

Promising results were achieved in several recently done human intervention studies. Within a 12-weeks intervention study (54 moderately overweighed individuals aged 40-65 years, BMI: 18.5-35) in the subgroup (n=18) with 70 mg lycopene per week, comprised in a supplement, significantly decreased serum amyloid A levels were determined, showing reduced inflammation (McEneny et al., 2012). Uptake of an optimized soup (7.6 mg lycopene per day) for four weeks (69 subjects aged 30 ± 10 years within two groups (optimized soup vs. control soup) resulted in significantly reduced levels of serum oxLDL (oxidized LDL cholesterol) (Martínez-Tomás et al., 2012). Daily consumption of 160 g tomato sauce high in lycopene (27.2 mg/d) for four weeks (30 healthy subjects aged 39 ± 6 years, BMI: 24.5 ± 3.3 kg/m^2) also induced a significant reduction in oxLDL levels in plasma (Abete et al., 2012). Daily consumption of 70 g tomato paste (33.3 mg lycopene per day) for two weeks (19 healthy subjects aged 39 ± 13 years, BMI:

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24.8 ± 4.4 kg/m^2) led to an increase in flow-mediated dilatation by 3.3%, thus improved endothelial function (Xaplanteris et al., 2012). In another recent study, 25 healthy subjects (27 ± 8 y, BMI: 22 ± 2 kg/m^2) consumed a high-fat meal (46% of energy from fat) together with 94 g tomato paste (27 mg lycopene) or without any tomato product. Compared to the control, the consumption of the tomato product significantly inhibited high-fat-induced postprandial oxidative and inflammatory responses (Burton-Freeman et al., 2012).

Conclusion

Chemical and *in vitro* cell studies have shown preventive properties of lycopene, being a potent antioxidant, against a variety of ROS and RNS. In addition, the epidemiologic studies suggest that consumption of tomato-based foods may lower CVD risk. Such potential benefits have been ascribed in part to high concentrations of lycopene in the tomatoes. However, these findings have yet only been supported by a small number of intervention trials. By defining the right population and combining antioxidant potentials of lycopene with vitamins and other bioactive plant compounds, the beneficial role of lycopene in CVD could be better clarified in future studies.

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Figure legends

Figure 1

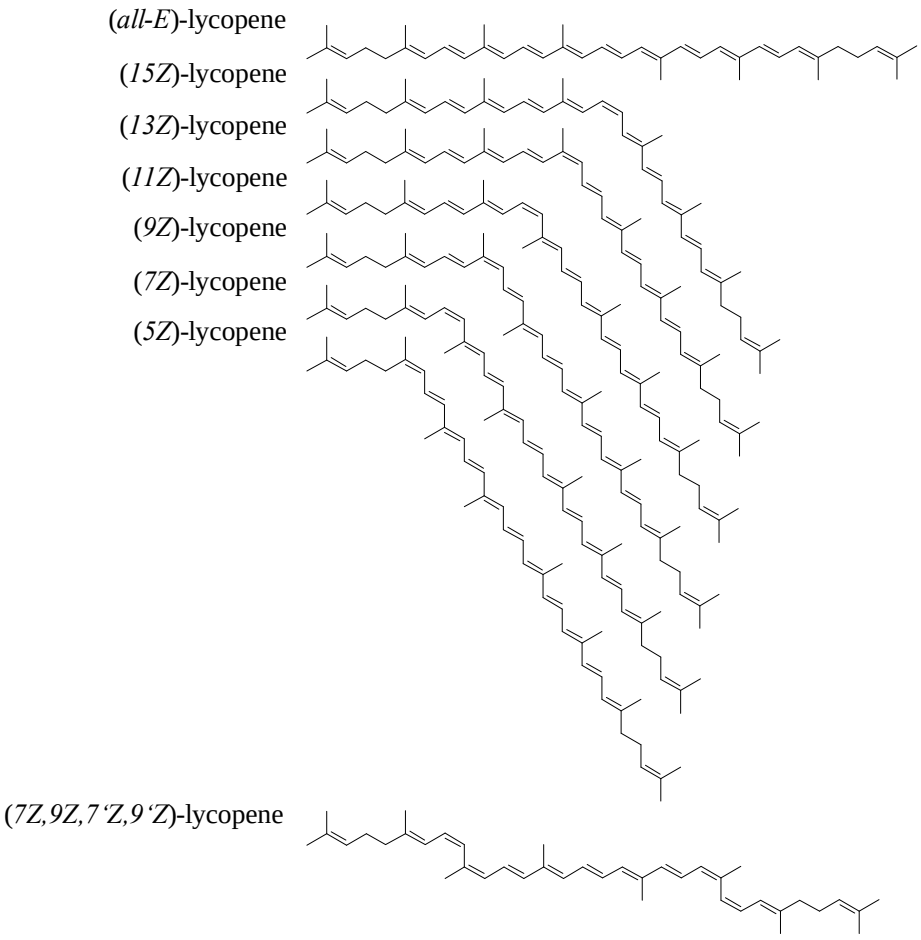

Figure 1: (*all-E*)-Isomer and some (*Z*)-isomers of lycopene