Carotenoids Regulate Endothelial Functions and Reduce the Risk of Cardiovascular Disease

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Abstract

Regular consumption of fruits and vegetables can help reduce the risk for cardiovascular disease (CVD) and its associated mortality. A diet rich in fruits and vegetables is thought to have cardioprotective effects, but the specific components of these foods that provide this protection are unclear. Antioxidants such as vitamin C, carotenoids, and polyphenols in fruits and vegetables likely contribute to the reduction in risk of CVD by minimizing cholesterol oxidation in blood vessel walls. Meanwhile, cardioprotective effects afforded by the carotenoids lycopene, α-carotene, β-carotene, β-cryptoxanthin, lutein, and zeaxanthin have been reported in many studies. Carotenoids are naturally occurring fat-soluble pigments that are present at high levels in tomatoes and carrots. Carotenoids play an important role in staving off atherosclerosis via antioxidant activities that reduce lipid peroxidation in low-density lipoproteins. Lycopene reduces endothelin-1 gene expression by suppressing generation of reactive oxygen species and inducing heme oxygenase-1 expression in human endothelial cells. Thus, carotenoids may mitigate endothelial dysfunction by promoting direct antioxidative effects and inducing expression of several genes. Structural and functional differences among carotenoids may explain their unique biologic activities. In this review, the roles of carotenoids in relation to their influence on vascular endothelial functions and cardioprotective effects are discussed.

Keywords: carotenoids, cardiovascular disease, endothelial cells

1. Introduction

Cardiovascular disease (CVD) is a common disease that has high mortality. Many epidemiological studies indicate that a diet rich in fruits and vegetables can have preventive effects for the development of CVD [1, 2]. As such, sufficient consumption of fruits and vegetables is recommended to ensure that vitamins, fiber, potassium, folate, and phenolic molecules are present.
in proper amounts to yield health benefits [3]. Several of these nutritive components have antioxidant activity and can modify lipoprotein profiles as well as increase insulin sensitivity, and lower blood pressure [4, 5]. Although carotenoids in particular are thought to provide health benefits, several studies suggested that these preventative effects may not be due to \( \beta \)-carotene and vitamin E present in fruits and vegetables [6]. In fact, some reports demonstrated that other carotenoids such as lycopene in tomatoes have preventive effects for CVD [7, 8].

Dietary carotenoids primarily come from fruits and vegetables, as well as plant seeds, roots, leaves, and flowers. Among 12 types of dietary carotenoids, particularly \( \alpha \)-carotene, \( \beta \)-carotene, lycopene, lutein, \( \beta \)-cryptoxanthin, and zeaxanthin, can be found in human blood and tissue samples [9, 10], and these molecules have similar chemical constitutions (Figure 1) and health benefits [11] (Table 3). \( \alpha \)-Carotene, \( \beta \)-carotene, \( \gamma \)-carotene, lycopene, and \( \beta \)-cryptoxanthin are all precursors of vitamin A. These carotenoids also have other beneficial effects beyond their antioxidant activity [12, 13].

Vascular endothelial cell disorders are a hallmark CVD. Several epidemiologic studies indicate that carotenoids can have a beneficial effect on vascular endothelial cell dysfunction. For example, in experiments using cultured vascular endothelial cells, carotenoids regulated nitric oxide (NO) expression and endothelin-1 (ET-1) production [14]. Moreover, lycopene inhibits expression of lipopolysaccharide (LPS)-enhanced monocyte chemoattractant protein-1 (MCP-1), interleukin-6 (IL-6), and vascular cell adhesion molecule-1 (VCAM-1) in human endothelial cells [14].

![Chemical structures of several carotenoids.](image)

Figure 1. Chemical structures of several carotenoids.
In contrast, lycopene reduced expression of TNF-α–induced intercellular adhesion molecule-1 (ICAM-1) and adhesion of monocyte endothelial cells [15]. In streptozotocin (STZ)-induced diabetic rats, lycopene inhibited endothelial dysfunction [16]. However, the in vitro effects of dietary carotenoids do not always translate to an in vivo setting. In the present review, we discuss the influence of carotenoids on vascular endothelial functions. Furthermore, we summarize evidence that carotenoids may have a preventive benefit toward CVD.

2. Source and bioactivity of natural carotenoids

Carotenoids are found as α-carotene, β-carotene, lycopene, lutein, β-cryptoxanthin, and zeaxanthin. Carotenoids are tetraterpenoids and are synthesized in plants such as vegetables and fruits as well as by other photosynthetic organisms and some nonphotosynthetic bacteria, yeasts, and molds [17]. Carotenoids confer the orange, yellow, and red color of many fruits and vegetables. Carotenoids can be classified as carotenes and xanthophylls according to the chemical structure. Xanthophylls contain oxygen, whereas carotenes are purely hydrocarbons and lack oxygen. The structures of common carotenoids are shown in Figure 1. β-Carotene is the most commonly found carotenoid in raw vegetables, canned fruits, and cooked vegetables [13]. Lycopene is present in tomato-based foods, including tomato paste, catsup, and other processed tomato products. Zeaxanthin and lutein are found in cooked kale and spinach and in a number of processed spinach products. Carotenoids can also be found in insects, fish, and crustaceans. The main sources and contents of dietary carotenoids are listed in Tables 1 and 2 [13, 18]. Carotenoids can be classified into pro-vitamin A and nonpro-vitamin A groups [19]. Daily vitamin A intake is dependent on the pro-vitamin A content of foods. In developing countries, approximately 70% of vitamin A intake is derived from carotenoids found in vegetables and fruits [17]. Pro-vitamin A is converted into vitamin A in the body via mechanisms that are not fully characterized, such that for purposes of bioequivalence, vitamin A levels are quantified according to vitamin A intake. Moreover, conversion efficiencies from carotenoid to vitamin A may influence the biological activity of carotenoids [20].

| Carotenoid          | Source                                             |
|--------------------|----------------------------------------------------|
| β-Carotene         | Carrots, apricots, mangoes, red pepper, kale, spinach, broccoli |
| α-Carotene         | Carrots, collard greens, pumpkin, corn, yellow pepper |
| β-Cryptoxanthin    | Avocado, oranges, papaya, passion fruit, pepper, persimmon |
| Lutein plus zeaxanthin | Kale, spinach broccoli, peas, brussels sprouts, collard greens, lettuce, corn, egg yolk |
| Lycopene           | Tomato and tomato products, watermelon, pink grapefruit, papaya, guava, rose hip |

Voutilainen et al. [17].

Table 1. Sources of dietary carotenoids.
| Carotenoids       | Food                        | Content (mg/100 g wet wt)* |
|-------------------|-----------------------------|-----------------------------|
| β-Carotene        | Carrots, raw                | 18.3                        |
|                   | Mangos, canned              | 13.1                        |
|                   | Sweet potato, cooked        | 9.5                         |
|                   | Carrots, cooked             | 8.0                         |
|                   | Pumpkin, canned             | 6.9                         |
|                   | Kale, cooked                | 6.2                         |
|                   | Spinach, cooked             | 5.2                         |
|                   | Winter butternut squash     | 4.6                         |
|                   | Swiss chard, raw            | 3.9                         |
|                   | Apricots, raw               | 2.6                         |
|                   | Pepper, red, raw            | 2.4                         |
|                   | Pepper, red, cooked         | 2.2                         |
|                   | Cantaloupe, raw             | 1.6                         |
|                   | Lettuce, romaine, raw       | 1.3                         |
|                   | Tomato paste                | 1.2                         |
| Lycopene          | Tomato paste                | 29.3                        |
|                   | Catsup                      | 17.0                        |
|                   | Tomato puree                | 16.7                        |
|                   | Pasta sauce                 | 16.0                        |
|                   | Tomato sauce                | 15.9                        |
|                   | Tomato soup                 | 10.9                        |
|                   | Tomato, canned, whole       | 9.7                         |
|                   | Tomato juice                | 9.3                         |
|                   | Watermelon, raw             | 4.9                         |
|                   | Tomato, cooked              | 4.4                         |
|                   | Tomato, raw                 | 3.0                         |
Many epidemiologic studies showed that carotenoids have beneficial effects toward CVD (Table 3). A cohort study that included 91,379 men, 129,701 women, and 5007 coronary heart disease events showed that fruits and vegetables intake was associated with decreased levels
of coronary heart disease [2]. Meanwhile, another large cohort study indicated that fruits and vegetables intake can reverse coronary heart disease [21]. Many epidemiological studies indicated that higher serum carotenoid levels have beneficial effects on CVD biomarkers. For example, lycopene intake was associated with decreased levels of CVD in a study of 314 CVD patients, 171 CHD patients, and 99 stroke patients [22]. Hazard ratios (HRs) for CVD onset were inversely correlated with lycopene intake. Another study that examined the intake of dietary carotene by 1312 men and 1544 women showed that dietary lutein and zeaxanthin consumption was clearly related to CVD onset, risk ratios, and biomarker levels such as HDL cholesterol [23]. A significant inverse relationship between LDL cholesterol and

| Intake from dietary | Study name | Nationality of subjects | Follow-up, Time | The number of subjects | Sex | Outcome (main results) | Reference (author, issue year) |
|---------------------|------------|-------------------------|-----------------|-----------------------|-----|------------------------|-------------------------------|
| Carotenoids with provitamin A activity | Finnish Mobile Clinic Study | Finnish | Prospective, 14 y | 5133 | F, M | Coronary mortality (nonsignificant inverse association between dietary intake of carotenoids with provitamin A activity and the risk of coronary mortality in women) | Knekt et al., 1994 |
| Carotenoids with provitamin A activity | ARIC study | American | Cross-sectional | 12,773 | F, M | Prevalence of carotid plaques (those in the highest quintile of carotenoid consumption had a lower prevalence of plaques) | Kritchevsky et al., 1998 |
| β-Carotene | The Rotterdam study | Dutch | Prospective, 4 y | 4802 | F, M | Myocardial infarction (significantly decreased risk of myocardial infarction in highest β-carotene intake quartile) | Klipstein-Grobusch et al., 1999 |
| β-Carotene, lutein plus zeaxanthin, and lycopene | ATBC study | Finnish | Prospective, 6.1 y | 26,593 | M | Stroke (dietary intake of β-carotene was inversely associated with the risk of cerebral infarction) | Hirvonen et al., 2000 |
| α- and β-Carotene, lutein, zeaxanthin, lycopene, and cryptoxanthin | Nurses Health Study | American | Prospective, 12 y | 73,286 | F | Coronary artery disease (inverse significant associations between the highest quintiles of intake of α-carotene and β-carotene and risk of coronary artery disease) | Osganian et al., 2003 |

Voutilainen et al. [17].

Table 3. Epidemiological studies of the effect on cardiovascular disease and atherosclerosis with carotenoids.
β-carotene, lutein, and zeaxanthin consumption as well as levels of dietary β-carotene and homocysteine was observed, whereas serum β-carotene affected the relationship between dietary β-carotene intake and C-reactive protein (CRP) levels. Given that hyperlipidemia, serum CRP, and homocysteine are CVD onset risk factors, serum carotenoids may be markers of dietary carotenoid uptake and CVD risk biomarkers. Indeed, a report by Sesso et al. [7] found that higher plasma lycopene levels were associated with decreased risk of CVD in a survey of 39,876 elderly women. In addition, a prospective study indicated that plasma α-carotene, β-carotene, and lycopene levels were associated with the risk of ischemic stroke [24]. A population-based follow-up study in Japan that examined the relationship between CVD and carotene concentration in 3061 subjects showed that higher serum total carotene levels, including α- and β-carotene and lycopene levels were associated with a reduced risk of CVD mortality [8]. Furthermore, report the inverse significant associations between the highest quintiles of the intake of α-carotene and β-carotene and risk of coronary artery disease [25]. In addition, dietary intake of β-carotene was inversely associated with the risk of cerebral infarction [26].

Marine animals produce the carotenoid astaxanthin that is known to have strong antioxidant activity. A study of 24 volunteers that consumed increasing doses of astaxanthin over the course of 14 days showed inhibition of LDL oxidation relative to control subjects that did not consume astaxanthin [27].

In contrast, other reports indicated that fruits and vegetables consumption is not associated with a reduced risk of coronary heart disease [28]. In a study of overweight adults at high risk for CVD, no dose-dependent reduction in CVD risk factors was seen with increased fruits and vegetables intake [29]. These results indicate that there may be some restrictions in the degree of protection afforded by carotenoids [30]. Moreover, a study of healthy adult subjects showed no effects of lutein, lycopene, or β-carotene on biological markers of oxidative stress, including LDL oxidation [31]. In a prospective study, the relationship between plasma lycopene concentration and CVD risk in 499 men showed that higher plasma lutein, zeaxanthin, and retinol levels were associated with a moderate increase in CVD risk, whereas β-cryptoxanthin, α-carotene, and β-carotene were not associated with increased risk of CVD [32]. Likewise, a prospective study involving a population of male physicians in the United States showed that high plasma levels of retinol and carotenoids had no protective effect toward myocardial infarction [33]. Moreover, four extensive, randomized studies revealed no decrease in CVD events by β-carotene treatment [34, 35]. These conflicting results again suggest that the reduction in the risk of CVD associated with fruits and vegetables intake is so far largely confined to observational epidemiology [30].

4. Protective effects of carotenoid-enriched foods

4.1. Tomato carotenoids

Tomato intake has been hypothesized to prevent endothelial dysfunction. However, one study involving 19 postmenopausal women who ingested tomato puree had increased
plasma lycopene levels, but no changes in artery dilation, which suggested that lycopene may not have direct effects on endothelial function [36]. On the other hand, another report demonstrated that tomato extract enhanced nitric oxide (NO) production and decreased endothelin release. These effects of tomato extract were related to suppression of inflammatory NF-κB signaling and prevention of adhesion molecule expression in endothelial cells [37], whereas tomato paste supplementation modified endothelial dysfunction and affected oxidation markers in the plasma of healthy human volunteers enrolled in a recent study [38]. Thus, these studies indicated that tomato paste intake can induce beneficial outcomes on endothelial function. The antioxidant properties of lycopene and β-carotene in tomato products may indeed regulate endothelial functions and protect against CVD. In a study that examined pigs with high cholesterol levels, consumption of a tomato-derived lycopene supplement maintained endothelial function of coronary arteries and regulated expression of apolipoprotein A-I and apolipoprotein J [39]. Lycopene supplementation also prevented vasoactive drug-induced coronary vasodilation and reduced lipid peroxidation, while enhancing high-density lipoprotein (HDL) levels and endothelial nitric oxide synthase (eNOS) expression. These results demonstrate that lycopene supplementation likely can protect against LDL-enhanced coronary endothelial dysfunction by augmenting endothelial nitric oxide (NO) expression and HDL levels as well as mediating leukocyte adhesion to endothelial cells in response to inflammation.

4.2. Carrot carotenoids

Carotenoids contained in carrots have beneficial health effects [40]. For example, drinking carrot juice induces antioxidant activity and reduces lipid peroxidation and can decrease levels of CVD risk markers in adults. In addition, carrot juice intake reduces systolic blood pressure [41]. Carrot juice consumption also improved glucose tolerance and hepatic structure and function, which might be associated with the effect of anthocyanins seen in metabolic syndrome [40, 42].

5. Preventive effects of carotenoids on cardiovascular disease associated with endothelial cell and macrophage dysfunction

Tomato paste supplementation regulated endothelial cell functions and prevented oxidative conditions in 19 healthy subjects [38]. Enhanced reactive oxygen species (ROS) generation is related to a functional inactivation of NO in endothelial cells and can induce CVD. β-Carotene and lycopene-mediated prevention of TNF-α expression was associated with reduced nitro-oxidative stress and inflammatory response in endothelial cells [43]. Meanwhile, in human endothelial cells, lycopene prevents endothelin-1 expression by inhibiting ROS generation and inducing heme oxygenase-1 expression (HO-1) [44], while also inhibiting tumor necrosis factor (TNF)-α–induced NF-κB activation, ICAM-1 expression, and monocyte endothelial adhesion [15]. In an in vivo study, lycopene inhibited endothelial dysfunction in STZ-enhanced diabetic rats by lowering oxidative stress, which could have implications for the development of treatments to prevent diabetic vascular complications [16]. In addition, astaxanthin inhibits inflammation-induced inducible NO and ROS generation by suppressing NF-κB pathway
activity in macrophages [45]. Thus, carotenoids could be effective for treating diseases associated with oxidative stress, such as CVD [46].

In vitro studies indicated that endothelial dysfunction induces atherogenic risk [47]. As shown in Table 4, carotenoids have a beneficial effect on endothelial cell function. In a study of healthy men, lycopene supplementation was suggested to inhibit oxidative stress-mediated decreases in endothelium function [48]. For example, lycopene prevents LPS-induced MCP-1, IL-6, and VCAM-1 expression in human endothelial cells [14]. Similarly, lycopene inhibits activity of an LPS-enhanced proinflammatory cytokine cascade in human endothelial cells through a mechanism that may involve increased expression of Krüppel-like factor 2 (KLF2) and inhibition of toll-like receptor (TLR) 4 function as well as downstream extracellular signal-regulated kinase (ERK) and NF-κB signaling in human endothelial cells [14].

As mentioned above, ET-1 is a strong vasopressor produced by endothelial cells. ET-1 levels may be affected by lycopene and in turn reduce the risk of CVD by modulating the activity of antiinflammatory pathways. Indeed, one report indicated that lycopene prevents cyclic strain-induced endothelin-1 expression by suppressing ROS production in human endothelial cells [44]. Furthermore, β-carotene and lycopene reduced TNF-α-enhanced inflammatory responses by reducing nitro-oxidative stress. These functions decreased interactions of endothelial cells with monocytes [43]. Another report demonstrated that β-carotene and lycopene treatment reduced TNF-α–induced oxidative stress and inflammatory responses to affect interactions between monocytes and human endothelial cells [43]. Furthermore, lycopene reduces C-reactive protein levels in CVD [49]. Meanwhile, paraoxonase-1 (PON1) prevents the oxidation of lipoproteins induced by oxidative stress and may induce metabolism of lipid peroxides [50]. We demonstrated that β-carotene decreases IL-1β–induced downregulation in PON1 expression by activating the CaMKII signaling pathway in human endothelial cells that may in turn produce antioxidant activity [51]. Similarly, astaxanthin reduces ROS induced-associated dysfunction in human endothelial cells exposed to glucose [52]. Astaxanthin inhibits streptozotocin-induced endothelial dysfunction in diabetes in male rats [53]. Astaxanthin also has antioxidant activity in human endothelial cells that is related to induction of p22phox expression and reduced peroxisome proliferator activated receptor-γ coactivator (PGC-1α) expression [54]. Together these activities of carotenoids may be responsible for their protective effect on CVD risk.

In cultured mouse macrophages, lutein-induced matrix metalloproteinase (MMP)-9 expression and phagocytosis promoted by intracellular ROS and activation of ERK1/2, p38 MAPK, and RAR β [55]. Furthermore, carotenoids induce increases in intracellular glutathione levels by elevating the activity of glutamate–cysteine ligase, the rate limiting enzyme in GSH synthesis [56]. In addition, preventive effects of β-carotene are associated with the β-carotene cleavage enzyme β-carotene 15,15′-monooxygenase (BCMO1) [57]. In the human macrophage cell line THP-1, β-carotene inhibited 7-ketocholesterol (7KC)-induced apoptosis by reducing expression levels of p53, p21, and Bax and inducing expression of AKT, Bcl-2, and Bcl-xL. Concomitantly, 7KC induced ROS generation with enhanced expression of NAD(P)H oxidase (NOX4). However, β-carotene blocked 7KC-induced ROS generation by inhibiting NOX4 [58]. Together these results indicate a possible antiarteriosclerotic action of β-carotene mediated
| Carotenoids | Preventive effects                                                                 | Mechanism of effects                                                                 | Experiment procedure | Reference (author, issue year)                        |
|------------|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|----------------------|-------------------------------------------------------|
| β-Carotene | Reverses the IL-1β-induced decrease in paraoxonase-1 expression                    | Induction of the CaMKKII pathway                                                    | In vitro             | Yamagata et al., 2012                                 |
|            | Prevent the TNFα-induced decrease nitro-oxidative stress and interaction with monocytes | Prevention of induced, inflammation, decrease of ROS generation, increased NO/cGMP levels and reduces NF-κB-dependent adhesion molecule expression | In vitro             | Di et al., 2012                                      |
| Lycopene   | Inhibited endothelin-1 expression and induces heme oxygenase-1                     | Block of ROS generation through NAD(P)H oxidase activity                            | In vitro             | Sung et al., 2015                                    |
|            | Improved endothelium-dependent vasodilation                                         | Low C-reactive protein levels in CVD and health volunteer                           | In vivo              | Gajendragadkar et al., 2014                          |
|            | Increase endothelial function                                                       | Reduce oxidative stress, low C-reactive protein levels and decreased ICAM-1, VCAM-1 | In vivo              | Kim et al., 2011                                     |
|            | Reduce proinflammatory cytokine cascade                                              | Inhibit TLR4 and NF-kappaB signaling pathway                                         | In vitro             | Wang et al., 2013                                    |
| Astaxanthin| Protect against glucose fluctuation.                                                | Reduced ROS generation                                                              | In vitro             | Abdelzaher et al., 2016                               |
|            | Ameliorative effect on endothelial dysfunction in streptozotocin-induced diabetes rats. Reduced serum oxLDL and aortic MDA. Reduced endothelium-dependent vasodilator with ACh. | Inhibition of the ox-LDL/LOX-1-eNOS pathway                                          | In vivo              | Zhao et al., 2011                                    |

ACh: acetylcholine; cGMP: cyclic GMP; CVD: cardiovascular disease; IL-1: interleukin-1; ICAM-1: intercellular adhesion molecule-1; LOX-1: lectin-like oxidized low density lipoprotein (LDL) receptor-1; MDA: malondialdehyde; NO: nitric oxide; oxLDL: oxidized low-density lipoprotein; TLR4: Toll-like receptor 4; TNFα: tumor necrosis factor-alpha; VCAM-1: vascular cell adhesion molecule-1.

Table 4. Preventive effect of carotenoids on vascular endothelial cells and macrophages.
through 7KC in human macrophages. β-Carotene also prevents expression of inflammatory
genes such as inducible NO synthase (iNOS), cyclooxygenase-2 (COX2), TNF-α, and IL-1 in
LPS-enhanced macrophages by inhibiting redox-related NF-κB activation [59].

6. Conclusions

This review examined the protective effects of carotenoids on CVD and the beneficial health
effects of dietary carotenoids. Many studies indicated that carotenoids exhibit bioactivity in
vascular endothelial cells. Carotenoids have antioxidant activity and appear to support and
maintain normal vascular endothelial cell function. Future research may reveal new beneficial
effects of carotenoids and help elucidate their preventive mechanisms in CVD.

Abbreviation

CVD cardiovascular disease
ET-1 endothelin-1
eNOS endothelial nitric oxide synthase
ERK extracellular signal-regulated kinases
HDL high-density lipoprotein
HO-1 heme oxygenase-1
ICAM-1 intercellular adhesion molecule-1
IL-6 interleukin-6
iNOS inducible NO synthase
7KC 7-ketocholesterol
KLF2 Krüppel-like factor 2
LDL low-density lipoprotein
LPS lipopolysaccharide
MCP-1 monocyte chemoattractant protein-1
MMP matrix metalloproteinase
NO nitric oxide
ROS reactive oxygen species
PON1 paraoxonase-1
PGC-1α peroxisome proliferator activated receptor-γ coactivator
TLR toll-like receptor
VCAM-1 vascular cell adhesion molecule-1
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References

[1] Pereira MA, O’Reilly E, Augustsson K, Fraser GE, Goldbourt U, Heitmann BL, Hallmans G, Knekt P, Liu S, Pietinen P, Spiegelman D, Stevens J, Virtamo J, Willett WC, Ascherio A: Dietary fiber and risk of coronary heart disease: A pooled analysis of cohort studies. Arch Intern Med. 2004;164:370–376.

[2] Dauchet L, Amouyel P, Hercberg S, Dallongeville J: Fruit and vegetable consumption and risk of coronary heart disease: A meta-analysis of cohort studies. J Nutr. 2006;136:2588–2593.

[3] Van Duyn MA, Pivonka E: Overview of the health benefits of fruit and vegetable consumption for the dietetics professional: Selected literature. J Am Diet Assoc. 2000;100:1511–1521.

[4] Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Sacks FM, Bray GA, Vogt TM, Cutler JA, Windhauser MM, Lin PH, Karanja N: A clinical trial of the effects of dietary patterns on blood pressure. DASH collaborative research group. N Engl J Med. 1997;336:1117–1124.

[5] Bazzano LA, Serdula MK, Liu S: Dietary intake of fruits and vegetables and risk of cardiovascular disease. Curr Atheroscler Rep. 2003;5:492–499.

[6] Bruckdorfer KR: Antioxidants and CVD. Proc Nutr Soc. 2008;67:214–222. DOI: 10.1017/S0029665108007052.

[7] Sesso HD, Buring JE, Norkus EP, Gaziano JM: Plasma lycopene, other carotenoids, and retinol and the risk of cardiovascular disease in women. Am J Clin Nutr. 2004;79:47–53.

[8] Ito Y, Kurata M, Suzuki K, Hamajima N, Hishida H, Aoki K: Cardiovascular disease mortality and serum carotenoid levels: A Japanese population-based follow-up study. J Epidemiol. 2006;16:154–160.

[9] Crews H, Alink G, Andersen R, Braesco V, Holst B, Maiani G, Ovesen L, Scotter M, Solfrizzo M, van den Berg R, Verhagen H, Williamson G: A critical assessment of some biomarker approaches linked with dietary intake. Br J Nutr. 2001;86 Suppl 1:S5-S35.

[10] Stahl W, Sies H: Lycopene: A biologically important carotenoid for humans? Arch Biochem Biophys. 1996;336:1–9.
[11] Gomes-Rochette NF, Da Silveira Vasconcelos M, Nabavi SM, Mota EF, Nunes-Pinheiro DC, Daglia M, De Melo DF: Fruit as potent natural antioxidants and their biological effects. Curr Pharm Biotechnol. 2016;17:986–993.

[12] Bendich A, Olson JA: Biological actions of carotenoids. FASEB J. 1989;3:1927–1932.

[13] Krinsky NI, Johnson EJ: Carotenoid actions and their relation to health and disease. Mol Aspects Med. 2005;26:459–516.

[14] Wang Y, Gao Y, Yu W, Jiang Z, Qu J, Li K: Lycopene protects against LPS-induced proinflammatory cytokine cascade in HUVECs. Pharmazie. 2013;68:681–684.

[15] Hung CF, Huang TF, Chen BH, Shieh JM, Wu PH, Wu WB: In endothelial cells, lycopene inhibited TNF-alpha-induced NF-kappaB activation, ICAM-1 expression and monocyte-endothelial adhesion. Eur J Pharmacol. 2008;586:275–282. DOI: 10.1016/j.ejphar.2008.03.001.

[16] Zhu J, Wang CG, Xu YG: Lycopene attenuates endothelial dysfunction in streptozotocin-induced diabetic rats by reducing oxidative stress. Pharm Biol. 2011;49:1144–1149. DOI: 10.3109/13880209.2011.574707.

[17] Stahl W, Sies H: Bioactivity and protective effects of natural carotenoids. Biochim Biophys Acta. 2005;1740:101–107.

[18] Voutilainen S, Nurmi T, Mursu J, Rissanen TH: Carotenoids and cardiovascular health. Am J Clin Nutr. 2006;83:1265–1271.

[19] Tang G: Vitamin A value of plant food provitamin A—Evaluated by the stable isotope technologies. Int J Vitam Nutr Res. 2014;84 Suppl 1:25–29. DOI: 10.1024/0300-9831/a000183.

[20] van Het Hof KH, West CE, Weststrate JA, Hautvast JG: Dietary factors that affect the bioavailability of carotenoids. J Nutr. 2000;130:503–506.

[21] Gan Y, Tong X, Li L, Cao S, Yin X, Gao C, Herath C, Li W, Jin Z, Chen Y, Lu Z: Consumption of fruit and vegetable and risk of coronary heart disease: A meta-analysis of prospective cohort studies. Int J Cardiol. 2015;183:129–137. DOI: 10.1016/j.ijcard.2015.01.077.

[22] Jacques PF, Lyass A, Massaro JM, Vasan RS, D’Agostino RB Sr: Relationship of lycopene intake and consumption of tomato products to incident CVD. Br J Nutr. 2013;110:545–551. DOI: 10.1017/S0007114512005417.

[23] Wang Y, Chung SJ, McCullough ML, Song WO, Fernandez ML, Koo SI, Chun OK: Dietary carotenoids are associated with cardiovascular disease risk biomarkers mediated by serum carotenoid concentrations. J Nutr. 2014;144:1067–1074. DOI: 10.3945/jn.113.184317.

[24] Hak AE, Ma J, Powell CB, Campos H, Gaziano JM, Willett WC, Stampfer MJ: Prospective study of plasma carotenoids and tocopherols in relation to risk of ischemic stroke. Stroke. 2004;35:1584–1588.
[25] Osganian SK, Stampfer MJ, Rimm E, Spiegelman D, Hu FB, Manson JE, Willett WC: Vitamin C and risk of coronary heart disease in women. J Am Coll Cardiol. 2003;42:246–252.

[26] Hirvonen T, Virtamo J, Korhonen P, Albanes D, Pietinen P: Intake of flavonoids, carotenoids, vitamins C and E, and risk of stroke in male smokers. Stroke. 2000;31:2301–2306.

[27] Iwamoto T, Hosoda K, Hirano R, Kurata H, Matsumoto A, Miki W, Kamiyama M, Itakura H, Yamamoto S, Kondo K: Inhibition of low-density lipoprotein oxidation by astaxanthin. J Atheroscler Thromb. 2000;7: 216–222.

[28] Woodside JV, Young IS, McKinley MC: Fruit and vegetable intake and risk of cardiovascular disease. Proc Nutr Soc. 2013;72: 399–406. DOI: 10.1017/S0029665113003029.

[29] McEvoy CT, Wallace IR, Hamill LL, Hunter SJ, Neville CE, Patterson CC, Woodside JV, Young IS, McKinley MC: increasing fruit and vegetable intake has no dose–response effect on conventional cardiovascular risk factors in overweight adults at high risk of developing cardiovascular disease. J Nutr. 2015;145:1464–1471. DOI: 10.3945/jn.115.213090

[30] Wallace IR, McEvoy CT, Hunter SJ, Hamill LL, Ennis CN, Bell PM, Patterson CC, Woodside JV, Young IS, McKinley MC: Dose–response effect of fruit and vegetables on insulin resistance in people at high risk of cardiovascular disease: A randomized controlled trial. Diabetes Care. 2013;36: 3888–3896. DOI. 10.2337/dc13-0718.

[31] Hininger IA, Meyer-Wenger A, Moser U, Wright A, Southon S, Thurnham D, Chopra M, Van Den Berg H, Olmedilla B, Favier AE, Roussel AM: No significant effects of lutein, lycopene or beta-carotene supplementation on biological markers of oxidative stress and LDL oxidizability in healthy adult subjects. J Am Coll Nutr. 2001;20:232–238.

[32] Sesso HD, Buring JE, Norkus EP, Gaziano JM: Plasma lycopene, other carotenoids, and retinol and the risk of cardiovascular disease in men. Am J Clin Nutr. 2005;81: 990–997.

[33] Hak AE, Stampfer MJ, Campos H, Sesso HD, Gaziano JM, Willett W, Ma J: Plasma carotenoids and tocopherols and risk of myocardial infarction in a low-risk population of US male physicians. Circulation. 2003;108: 802–807.

[34] The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. N Engl J Med. 1994;330:1029–1035.

[35] Hennekens CH, Buring JE, Manson JE, Stampfer M, Rosner B, Cook NR, Belanger C, LaMotte F, Gaziano JM, Ridker PM, Willett W, Peto R: Lack of effect of long-term supplementation with beta carotene on the incidence of malignant neoplasms and cardiovascular disease. N Engl J Med. 1996;334:1145–1149.

[36] Stangl V, Kuhn C, Hentschel S, Joachmann N, Jacob C, Bohm V, Frohlich K, Muller L, Gericke C, Lorenz M: Lack of effects of tomato products on endothelial function in human subjects: Results of a randomised, placebo-controlled cross-over study. Br J Nutr. 2011;105:263–267. DOI: 10.1017/S0007114510003284.
[37] Armoza A, Haim Y, Bashiri A, Wolak T, Paran E: Tomato extract and the carotenoids lycopene and lutein improve endothelial function and attenuate inflammatory NF-κB signaling in endothelial cells. J Hypertens. 2013;31:521–529. DOI: 10.1097/HJH.0b013e32835c1d01.

[38] Xaplanteris P, Vlachopoulos C, Pietri P, Terentes-Printzios D, Kardara D, Alexopoulos N, Aznaouridis K, Miliou A, Stefanadis C: Tomato paste supplementation improves endothelial dynamics and reduces plasma total oxidative status in healthy subjects. Nutr Res. 2012;32:390–394. DOI: 10.1016/j.nutres.2012.03.011.

[39] Vilahur G, Cubedo J, Padro T, Casani L, Mendieta G, Gonzalez A, Badimon L: Intake of cooked tomato sauce preserves coronary endothelial function and improves apolipoprotein A-I and apolipoprotein J protein profile in high-density lipoproteins. Transl Res. 2015;166:44–56. DOI: 10.1016/j.trsl.2014.11.004.

[40] Sharma KD, Karki S, Thakur NS, Attri S: Chemical composition, functional properties and processing of carrot-a review. J Food Sci Technol. 2012;49:22–32. DOI: 10.1007/s13197-011-0310-7.

[41] Potter AS, Foroudi S, Stamatikos A, Patil BS, Deyhim F: Drinking carrot juice increases total antioxidant status and decreases lipid peroxidation in adults. Nutr J. 2011 Sep 24;10:96. DOI: 10.1186/1475-2891-10-96.

[42] Poudyal H, Panchal S, Brown L: Comparison of purple carrot juice and β-carotene in a high-carbohydrate, high-fat diet-fed rat model of the metabolic syndrome. Br J Nutr. 2010;104:1322–1332. DOI: 10.1017/S0007114510002308.

[43] Di Tomo P, Canali R, Ciavardelli D, Di Silvestre S, De Marco A, Giardinelli A, Pipino C, Di Pietro N, Virgili F, Pandolfi A: β-Carotene and lycopene affect endothelial response to TNF-α reducing nitro-oxidative stress and interaction with monocytes. Mol Nutr Food Res. 2012;56:217–227. DOI:10.1002/mnfr.201100500.

[44] Sung LC, Chao HH, Chen CH, Tsai JC, Liu JC, Hong HJ, Cheng TH, Chen JJ: Lycopene inhibits cyclic strain-induced endothelin-1 expression through the suppression of reactive oxygen species generation and induction of heme oxygenase-1 in human umbilical vein endothelial cells. Clin Exp Pharmacol Physiol. 2015;42:632–639. DOI: 10.1111/1440-1681.12412.

[45] Lee SJ, Bai SK, Lee KS, Namkoong S, Na HJ, Ha KS, Han JA, Yim SV, Chang K, Kwon YG, Lee SK, Kim YM: Astaxanthin inhibits nitric oxide production and inflammatory gene expression by suppressing I (kappa)B kinase-dependent NF-kappaB activation. Mol Cells. 2003;16:97–105.

[46] Sies H, Stahl W, Sundquist AR: Antioxidant functions of vitamins. Vitamins E and C, beta-carotene, and other carotenoids. Ann N Y Acad Sci. 1992;30;669:7–20.

[47] Shimokawa H: Primary endothelial dysfunction: atherosclerosis. J Mol Cell Cardiol. 1999;31:23–37.
[48] Kim JY, Paik JK, Kim OY, Park HW, Lee JH, Jang Y, Lee JH: Effects of lycopene supplementation on oxidative stress and markers of endothelial function in healthy men. Atherosclerosis. 2011; 215:189–195. DOI: 10.1016/j.atherosclerosis.2010.11.036.

[49] Gajendragadkar PR, Hubsch A, Maki-Petaja KM, Serg M, Wilkinson IB, Cheriyan J: Effects of oral lycopene supplementation on vascular function in patients with cardiovascular disease and healthy volunteers: A randomised controlled trial. PLoS One. 2014;9:e99070. DOI: 10.1371/journal.pone.0099070. eCollection 2014.

[50] Mackness MI, Arrol S, Abbott C, Durrington PN: Protection of low-density lipoprotein against oxidative modification by high-density lipoprotein associated paraoxonase. Atherosclerosis. 1993;104:129–135.

[51] Yamagata K, Tanaka N, Matsufuji H, Chino M: β-Carotene reverses the IL-1β-mediated reduction in paraoxonase-1 expression via induction of the CaMKII pathway in human endothelial cells. Microvasc Res. 2012;84: 297–305. DOI: 10.1016/j.mvr.2012.06.007.

[52] Abdelzaher LA, Imaizumi T, Suzuki T, Tomita K, Takashina M, Hattori Y: Astaxanthin alleviates oxidative stress insults-related derangements in human vascular endothelial cells exposed to glucose fluctuations. Life Sci. 2016;150:24–31. DOI: 10.1016/j.lfs.2016.02.087.

[53] Zhao ZW, Cai W, Lin YL, Lin QF, Jiang Q, Lin Z, Chen LL: Ameliorative effect of astaxanthin on endothelial dysfunction in streptozotocin-induced diabetes in male rats. Arzneimittelforschung. 2011; 61:239–246. DOI: 10.1055/s-0031-1296194.

[54] Regnier P, Bastias J, Rodriguez-Ruiz V, Caballero-Casero N, Caballo C, Sicilia D, Fuentes A, Maire M, Crepin M, Letourneur D, Gueguen V, Rubio S, Pavon-Djavid G: Astaxanthin from haematococcus pluvialis prevents oxidative stress on human endothelial cells without toxicity. Mar Drugs. 2015;13: 2857–2874. DOI: 10.3390/md13052857.

[55] Lo HM, Chen CL, Yang CM, Wu PH, Tsou CJ, Chiang KW, Wu WB: The carotenoid lutein enhances matrix metalloproteinase-9 production and phagocytosis through intracellular ROS generation and ERK1/2, p38 MAPK, and RARβ activation in murine macrophages. J Leukoc Biol. 2013;93:723–735. DOI: 10.1189/jlb.0512238

[56] Akaboshi T, Yamanishi R: Certain carotenoids enhance the intracellular glutathione level in a murine cultured macrophage cell line by inducing glutamate-cysteine-ligase. Mol Nutr Food Res. 2014;58: 1291–1300. DOI: 10.1002/mnfr.201300753.

[57] Zolberg Relevy N, Bechor S, Harari A, Ben-Amoz A, Kamari Y, Harats D, Shaish A: The inhibition of macrophage foam cell formation by 9-cis-β-carotene is driven by BCMO1 activity. PLoS One. 2015;10: e0115272. DOI: 10.1371/journal.pone.0115272.

[58] Palozza P, Simone R, Catalano A, Boninsegna A, Bohm V, Frohlich K, Mele MC, Monego G, Ranelletti FO: Lycopene prevents 7-ketocholesterol-induced oxidative stress, cell
cycle arrest and apoptosis in human macrophages. J Nutr Biochem. 2010;21:34–46. DOI:10.1016/j.jnutbio.2008.10.002.

[59] Bai SK, Lee SJ, Na HJ, Ha KS, Han JA, Lee H, Kwon YG, Chung CK, Kim YM: Beta-carotene inhibits inflammatory gene expression in lipopolysaccharide-stimulated macrophages by suppressing redox-based NF-kappaB activation. Exp Mol Med. 2005;37:323–334.
