Chapter 7

Carotenoids Regulate Endothelial Functions and Reduce the Risk of Cardiovascular Disease

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Additional information is available at the end of the chapter

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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 β-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 α-carotene, β-carotene, lycopene, lutein, β-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**). α-Carotene, β-carotene, γ-carotene, lycopene, and β-cryptoxanthin are all precursors of vitamin A. These carotenoids also have other beneficial effects beyond their antioxidant activity [12, 13].

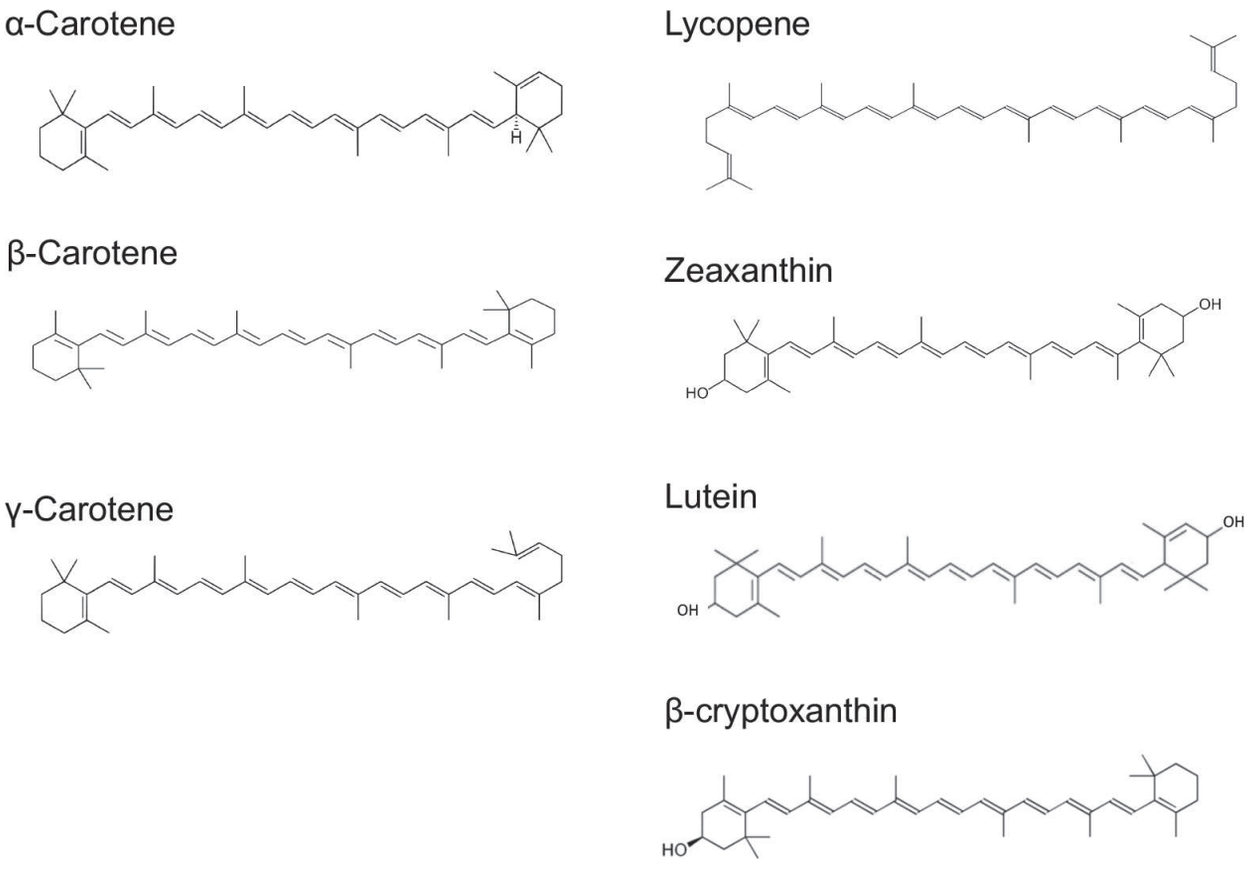

Figure 1. Chemical structures of several carotenoids.

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].

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)[a]
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

Carotenoids	Food	Content (mg/100 g wet wt)[a]
Lutein and zeaxanthin	Kale, cooked	15.8
	Spinach, raw	11.9
	Spinach, cooked	7.0
	Lettuce, romaine, raw	2.6
	Broccoli, raw	2.4
	Broccoli, cooked	2.2
	Summer squash, zucchini	2.1
	Corn, sweet, cooked	1.8
	Peas, green, canned	1.4
	Brussels sprouts, cooked	1.3
	Corn, sweet, canned	0.9
	Beans, green, cooked	0.7
	Beans, green, canned	0.7
	Beans, green, raw	0.6
	Okra, cooked	0.4
	Cabbage, white, raw	0.3
	Egg yolk, medium	0.3
	Celery, raw	0.2
	Orange, raw	0.2
	Tomato paste	0.2

[a]Edible portion.
Krinsky and Johnson [13].

Table 2. Carotenoid contents in foods.

3. Epidemiological studies of carotenoids

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 Rotterdan study	Dutch	Prospective, 4 y	4802	F, M	Myocardial infarction (significantly decreased risk of myocardial infarction in highest -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 αplus 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 linked 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 antioxidative 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 vitr*o 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 CaMKKII 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 vasodilatation	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.

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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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