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Tomatoes and Cardiovascular Health

Joye K. Willcox,[1] George L. Catignani,[1] and Sheryl Lazarus[2]*

[1]Dept. of Food Science, North Carolina State University, [2]Mars, Incorporated

Referee: **Dr. John Erdman, Director, Division of Nutrition and Food Science, University of Illinois, 455 Bevier Hall, 905 South Goodwin, Urbana, IL 61801**

* Corresponding author: North Carolina State University, Box 7624, Raleigh, North Carolina 27695-7624, USA.

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ABSTRACT: Diet is believed to play a complex role in the development of cardiovascular disease, the leading cause of death in the Western world. Tomatoes, the second most produced and consumed vegetable nationwide, are a rich source of lycopene, beta-carotene, folate, potassium, vitamin C, flavonoids, and vitamin E. The processing of tomatoes may significantly affect the bioavailability of these nutrients. Homogenization, heat treatment, and the incorporation of oil in processed tomato products leads to increased lycopene bioavailability, while some of the same processes cause significant loss of other nutrients. Nutrient content is also affected by variety and maturity. Many of these nutrients may function individually, or in concert, to protect lipoproteins and vascular cells from oxidation, the most widely accepted theory for the genesis of atherosclerosis. This hypothesis has been supported by *in vitro*, limited *in vivo*, and many epidemiological studies that associate reduced cardiovascular risk with consumption of antioxidant-rich foods. Other cardioprotective functions provided by the nutrients in tomatoes may include the reduction of low-density lipoprotein (LDL) cholesterol, homocysteine, platelet aggregation, and blood pressure. Because tomatoes include several nutrients associated with theoretical or proven effects and are widely consumed year round, they may be considered a valuable component of a cardioprotective diet.

KEY WORDS: antioxidant, atherosclerosis, lycopene.

I. INTRODUCTION

Cardiovascular disease is the leading cause of death in the U.S. and the third leading cause of global deaths. By 2010, cardiovascular disease is expected to be the leading cause of death in developing countries (World Health Organization, 2001). Diet is believed to play a major role in the development of this disease, and much interest and research are being focused on identifying ways to prevent it through dietary changes. Oxidation of unsaturated lipids in the low-density lipoprotein (LDL) particle is hypothesized to initiate a complex sequence of events that may lead to the development of atherosclerosis. It has been suggested that carotenoids, including β-carotene and lycopene, may protect lipoproteins and vascular cells from oxidation. This hypothesis has been supported by *in vitro*, limited *in vivo*, and many epidemiological studies that associate reduced cardiovascular risk with the consumption of carotenoid- and antioxidant-rich foods (Mayne, 1996).

The tomato probably originated in Peru and although introduced into Italy at the beginning of the sixteenth century as an ornamental plant, it did not begin to be grown for food until the middle of that century. Its cultivation has become widespread over the subsequent centuries and is now one of the world's major food crops (Frusciante et al., 2000). Tomatoes are a rich source of beta carotene, folate, potassium, vitamin C, vitamin E, flavonoids, and lycopene. Tomato products provide an estimated 80% of lycopene and are the fourth leading source of vitamin A in the U.S. diet.

Processing of tomatoes may significantly affect the bioavailability of lycopene. The cis isomeric form, found in processed tomato products, appears to be more bioavailable than the natural trans form (Rao and Agarwal, 1999).

II. CONSUMPTION PATTERNS

A. United States

Tomatoes are the second highest produced and consumed vegetable in the U.S. today. By 1999, this translated to approximately 17.6 pounds

of fresh and 72.8 pounds processed tomatoes annually per person. Both fresh and processed consumption has increased nearly 30% in our country over the last 2 decades. On any given day, approximately 60% of consumers report use of processed tomato products (Figure 1).

The majority of tomatoes and tomato products are purchased at retail stores and consumed at home, with the exception of catsup (Figure 2).

Per capita consumption of fresh tomatoes is slightly higher in the Northeast and the West and slightly less in the Midwest and South. The South has the lowest per capita consumption of processed tomato products, while the West and Midwest are the highest (Figure 3).

Non-Hispanic Black consumers have the lowest intake of fresh tomatoes, while Hispanics have the highest intake. Per capita consumption of fresh and processed tomato products increases with annual income (Lucier et al., 2000).

B. Global

The export of tomato products is becoming an important component of the U.S. processed tomato industry. During the 1990s, the U.S. became a net exporter of tomato products.

Canada is the leading consumer of U.S. processed tomato products, followed by Japan and Mexico. In 1999, 41% of the exported tomato products were sauces, 29% paste, 13% catsup, and 11% canned whole products. Fresh tomatoes are also predominantly shipped to Canada, followed by exportation to Mexico and Japan (Lucier, 2000).

The estimated production of selected products for several countries during 2000 is shown in Table 1 (USDA, 2001):

III. NUTRIENT COMPOSITION OF TOMATO PRODUCTS

A comparison of the major nutrients in selected tomato products is shown in Table 2.

A. Lycopene

Lycopene is an acyclic carotenoid with 11 linear conjugated double bonds, but lacks the

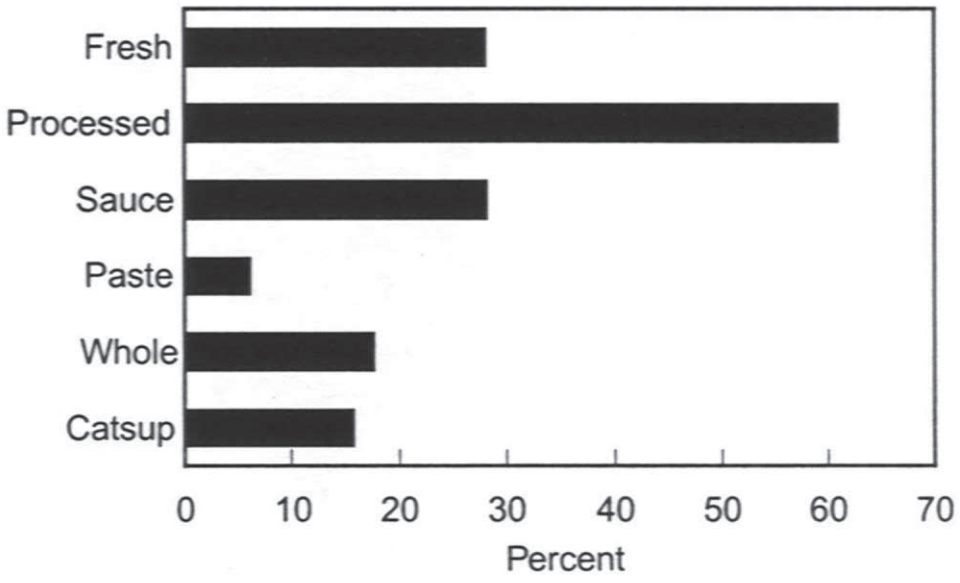
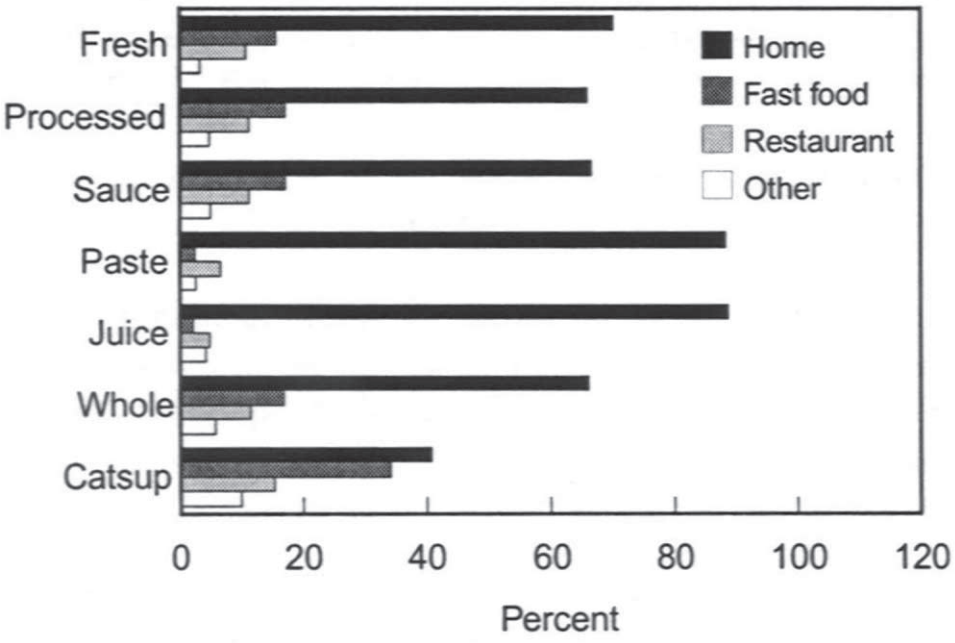
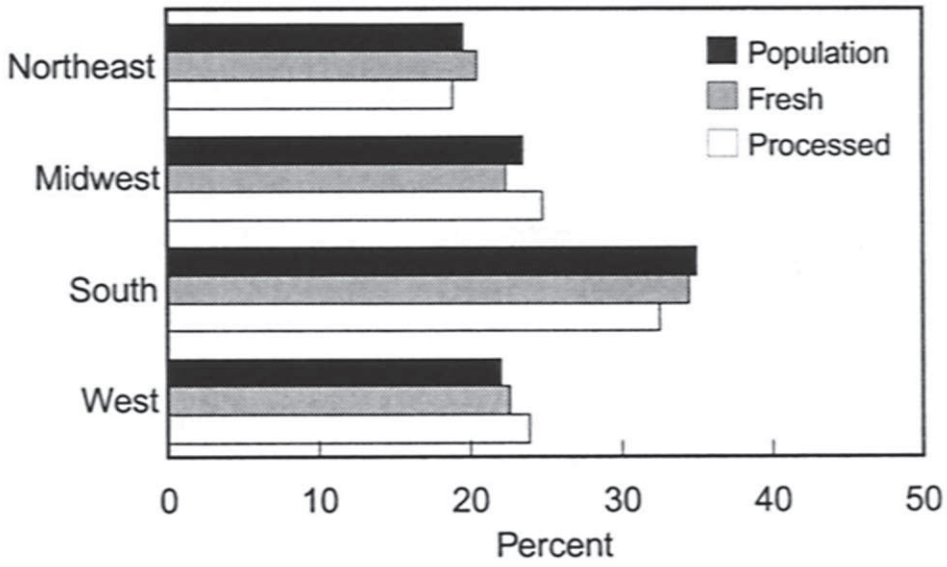


FIGURE 1. Percent of consumers reporting tomato use on any given day.



Source: Economic Research Service, USDA.

FIGURE 2. Consumption of tomatoes by location.



Source: Economic Research Service, USDA.

FIGURE 3. U.S. population and tomato consumption by region.

TABLE 1
Estimated Production of Tomato Products in 2000.

Country	Tomatoes for Processing	Tomato Paste
U.S.	9.3 million tons	
Mexico	210,000 tons	28,500 tons
Brazil	1.2 million tons	110,000 tons
Chile	925,000 tons	115,000 tons
France	370,000 tons	44,500 tons
Turkey	1.7 million tons	260,000 tons
Greece	1.2 million tons	184,500 tons
Spain	1.4 million tons	213,000 tons
Italy	4.7 million tons	340,000 tons
Portugal	885,000 tons	156,000 tons
Israel	260,000 tons	28,000 tons

Source: Economic Research Service, USDA, Briefing Room-Tomatoes.

TABLE 2
Comparison of Major Nutrients in Selected Tomato Products

Comparison of Major Nutrients in Selected Tomato Products

	DRI	Fr, Red	Fr, Yellow	Can, whole	Stewed	Soup, prep	Juice	Sauce	Puree	Paste	Catsup
Serv size		1/2 cup	1/2 cup	1/2 cup	1/2 cup	1 cup	1/2 c	1/2 c	1/2 c.	2 Tb.	1 Tb.
wt, gm.		90	90	120	128	244	122	122	125	33	17
Vitamin C	90/75*	17.2	8.1	17	23.3	66.4	22.3	16	13	13	2.6
mg.											
Vitamin A	900/700*	55.8	0	72	85.8	68.3	68.3	119	160	28.7	17.3
RAE											
α-carotene	n/a	101		0			0	0	0	10	
µg											
β-carotene	n/a	354		223			522	500	512	409	
µg											
Lycopene	n/a	2722		11649			11367	19417	20838	9679	
µg											
Lutein/Zea	n/a	117		48			73.2	1.22	112.5	56.1	
µg											
Potassium	3500	200	232	272	317	264	268	253	533	309	82
mg											
Folic Acid	400	13.5	27	9.4	5.5	14.6	24.3	11.5	13.8	7.4	2.6
µg											
Vitamin E	22	.34	-	.45	1.52	2.48	1.11	1.7	3.13	1.4	.22
IU											

Source: USDA NCC Carotenoid Database for U.S. Foods-1998, USDA Nutrient Database for Standard Ref., 1999.
DRI- Dietary Reference Intake, including 1999-2001 National Academy of Science recommendations for RDA and 1997-98 DRV (Daily Reference Value) n/a-no established recommended value. Fr-Fresh RAE-Retinol Activity Equivalent, 1RAE=1 µg retinol men/women*

β-ionone ring structure and therefore is devoid of vitamin A activity. These conjugated double bonds are susceptible to oxidation, thereby making lycopene a potent antioxidant chemically. Its linear hydrocarbon structure makes it hydrophobic and more likely to reside in lipid environments. More than 80% of dietary lycopene consumed in the U.S. comes from tomato products. The lycopene content of tomatoes fluctuates with season and variety, but remains relatively stable with processing (discussed later in more detail). For example, red tomatoes have approximately 50 mg lycopene/kg, compared with only 5 mg/kg in yellow varieties (Clinton, 1998).

Interest in lycopene continues to grow following the publication of epidemiological and clinical studies associating high lycopene blood levels with reductions in cardiovascular disease (CVD) incidence. Epidemiological studies also suggest that intimal wall thickness and risk of myocardial infarction are reduced in individuals with higher adipose tissue storage of lycopene.

The EURAMIC study, which evaluated myocardial infarction in men with matched controls in 10 European countries, found lycopene concentration of adipose tissue to be independently protective against myocardial infarction. The protective effect of lycopene was strongest among nonsmokers and in those with higher levels of polyunsaturated fat in the adipose tissue (Kohlmeier et al., 1997). In an earlier case controlled study, the investigators did not associate serum carotenoids with a lower risk of myocardial infarction (Street et al., 1994). A cross-sectional comparison of Lithuanian and Swedish populations found an association between lower serum lycopene levels and higher mortality from cardiovascular heart disease (Kristenson et al., 1997). An Austrian report showed that an elderly population measured lower serum lycopene and α-tocopherol levels in individuals at higher risk for cerebrovascular disease (Schmidt et al., 1997). A case-control analysis of 108 elderly subjects of the Rotterdam Study revealed an inverse association between serum lycopene and the presence of atherosclerosis, with the most pronounced effect seen in current and former smokers (Klipstein-Grobusch et al., 2000).

Four of the largest case-control studies published between 1994 and 1997 report odds ratios ranging from .39 to .81, which would translate to a 19 to 61% decrease in cardiovascular-related endpoints in individuals with higher lycopene levels (Arab and Steck, 2000). A baseline measurement preceding the ASAP (Antioxidant Supplementation in Atherosclerosis Prevention) Study concluded that lower plasma levels of lycopene were associated with early atherosclerosis, manifested as increased common carotid artery intima-media wall thickness in men (Rissanen et al., 2000). Cohort studies also show an association between blood lycopene levels and cardiovascular outcomes. The Kuopio Ischaemic Heart Disease Risk Factor Study showed an average 4% decrease in risk of acute coronary events for each 10 nmol/L increment increase of serum lycopene (Rissanen et al., 2001).

B. Vitamin C

Tomatoes and tomato juice are the third leading contributors of vitamin C in the American diet. Overall, tomatoes provide approximately 20 mg of vitamin C per 100 grams of edible product. Soup alone provides 74 to 88% of the current RDA of 90/75 mg (men/women). Vitamin C is considered an excellent antioxidant because it donates electrons for enzymes or other compounds that are oxidants. Unlike many antioxidants, its radical intermediate is relatively harmless because it reacts poorly with oxygen, producing little if any superoxide or other radicals and is readily reduced back to a form that can be reused (Levine et al., 1996).

The association of vitamin C intake and the prevention of cardiovascular disease has been investigated in both animal and human studies. The protection of LDL against oxidation appears to involve a sparing of the lipophilic antioxidant, tocopherol by vitamin C (Packer et al., 2001). Vitamin C deficiency has been shown to promote the formation of atherosclerotic lesions in guinea pigs, but evidence of this effect in humans is weak at present. Subjects in the first National Health and Nutrition Examination Survey (NHANES I) exhibiting the highest vitamin C

intakes had lower levels of cardiovascular disease compared with those with lower estimated intakes. However, other large observational studies have failed to find such a relationship (Combs, 1998a).

C. Potassium

High blood pressure is another major risk factor for cardiovascular disease. Potassium is known to lower blood pressure. Cross-sectional multicultural epidemiological studies have all identified an inverse relationship between blood pressure and potassium in the diet, urine, and serum. Two large meta-analyses involving a total of 55 human intervention trials found reduced systolic and diastolic blood pressures in subjects receiving potassium (Intersalt Cooperative Research Group 1988). Recently, more emphasis has been placed on getting adequate potassium in the diet along with calcium and magnesium to prevent and control high blood pressure.

D. Folic Acid

Folic acid, along with two vitamins, B6 and B12, help to metabolize and clear homocysteine, which, when elevated in plasma, is related to higher incidence of cardiovascular disease. Because of that relationship, the American Heart Association advises a healthy, balanced diet that includes five daily servings of fruits and vegetables and lists tomatoes as a good source of folic acid. Tomatoes and tomato products provide a range of 0.6 to 6% of the current 400 μg RDA.

A prospective cohort study involving 734 middle-aged men from Eastern Finland indicated that moderate to high levels of serum folate are associated with a greatly reduced incidence (69%) of acute coronary events (Voutilainen et al., 2000).

E. Other Carotenoids

Epidemiological studies have found inverse relationships between consumption of carotene-rich fruits and vegetables and risks of chronic diseases, including cardiovascular disease and stroke. Low β-carotene serum levels are associated with increased incidence of myocardial infarction in these studies. One study assessed the relationship between plasma carotenoids (α– and β-carotene, lutein, lycopene, zeaxanthin, β-cryptoxanthin), vitamins A and E, and atherosclerosis in carotid and femoral arteries. This prospective study included a total of 392 men and women aged 45 to 65. Atherosclerosis was determined by ultrasound. A strong inverse relationship was found between atherosclerosis and α and β carotene plasma levels while the other carotenoids showed a nonsignificant inverse relationship (D'Odorico et al., 2000). However, four well-designed randomized, double blind clinical trials have found β-carotene to be ineffective in reducing the risk of cardiovascular disease or angina pectoris. In fact, one study found an increased incidence of angina with β-carotene supplementation (Alpha-Tocopherol, Beta-Carotene Study Group, 1994) in heavy smokers. It has been suggested that low serum vitamin C levels in this group may lead to oxidative damage from high levels of β-carotene radical cations, which would normally be quenched by the availability of adequate vitamin C (Mortensen et al., 2001).

Animal studies support the hypothesis that dietary carotenoids protect against atherosclerosis (Shaish et al., 1995). Supplementation with β-carotene in smoking has been shown to improve antioxidant status as measured by pentane breath test in smokers and plasma malondialdehyde in subjects with cystic fibrosis. At low oxygen pressures, β-carotene can participate in quenching of free radicals, but because of their low concentration in tissues, its contribution to antioxidant protection *in vivo* continues to be investigated (Combs, 1998b).

F. Flavonoids

Flavonoids are phenolic antioxidant compounds formed in plants. Generally, they occur as glycosylated derivatives. Humans show a wide variation in flavonoid intake, depending on consumption patterns of fruits, vegetables, tea, certain chocolates, and red wine, the major sources

of these antioxidants. Flavonoids are synthesized and stored mainly in the skin of tomatoes and therefore are more concentrated in smaller varieties, such as the cherry or grape tomatoes. For example, cherry tomatoes contain an average 30 μg/g, whereas normal-sized varieties contain only 5 μg/g. Recently reported is the production of a transgenic tomato that over-expresses the enzyme, chalcone isomerase, derived from the petunia. The resulting plant produced tomato fruit with a 78-fold increase in peel flavonoids, of which the quercetin glycoside, rutin, was the most abundant (Muir et al., 2001). Flavonoids are effective antioxidants in a wide range of chemical oxidation systems *in vitro*. However, these phenolic antioxidants vary widely in their bioavailability. For example, the absorption of quercetin, the major flavonoid found in tomatoes, may range from 0 to 50% of the dose ingested. Much more research with improved analytical methodology is needed to determine the actual bioavailability of these compounds (Duthie and Crozier, 2000).

Recently, much research has focused on the antioxidant role of flavonoids in the human diet (Nijveldt et al., 2001). Flavonoids can directly and indirectly interfere with several free radical-generating systems. Flavonoids, with their reactive hydroxyl groups directly scavenge free radicals by being oxidized to a more stable and less reactive radical:

FLAV-OH + R·(free radical) → FLAV-O· + RH (neutralized free radical)

There are other mechanisms by which they act as antioxidants, such as chelating metal ions. Metal chelation is important because reactive oxygen species are converted to free radicals in the presence of iron.

Several flavonoids may reduce ischemia-reperfusion injury by minimizing the oxidative stress associated with the event. Nitric oxide can react with free radicals, such as superoxide, to produce the highly damaging peroxynitrite (Huk et al., 1998). If sufficient flavonoids are present, these radicals can be scavenged by the mechanism shown above, thereby decreasing the concentration of reactive species available for reactivity with nitric oxide. Likewise, the xanthine oxidase pathway has been implicated as a major route in the oxidative damage to tissues, especially following ischemia with subsequent reperfusion. At least two flavonoids, quercetin and silibin, inhibit xanthine oxidase activity, a major source of oxygen-free radicals during the reoxygenation phase following an ischemic event (Nijveldt et al., 2001).

Other proposed cardioprotective effects of flavonoids include: altering of endothelial cell eicosanoid production, a reduction of adhesion receptor expression, a reduction of platelet aggregation, and a decrease in LDL oxidation (Schramm and Germann, 1998). Figure 4, adapted from a recent review (Nijveldt et al., 2001), summarizes some hypothetical links between flavonoids and their effects on cardiovascular disease.

Several epidemiological studies have shown a protective effect of fruits and vegetables against heart disease and stroke. Flavonoids may provide some of this protective effect due in part to their antioxidant properties. This has been seen in several *in vitro*, *ex vivo*, and animal studies, but remains to be proven in human trials (Pietta, 2000). However, human epidemiological data are highly suggestive of a protective role for flavonoids against cardiovascular disease. Four of the six major epidemiological studies reported a possible protective role of flavonoid intake for coronary heart disease. The evidence is stronger for cardiovascular-related mortality than for morbidity (Hertog et al., 1998).

G. Vitamin E

Vitamin E is considered the main biological antioxidant in vivo and has been reviewed extensively (Jialal et al., 2001). α-Tocopherol is a chain-breaking lipid-soluble antioxidant that traps peroxyl free radicals. A relationship between low α-tocopherol levels and the development of atherosclerosis has been shown through several lines of evidence. Aside from being a potent antioxidant, as evidenced by decreased LDL oxidative susceptibility and oxidation end products, α-tocopherol has been shown to hinder platelet aggregation and adhesion, decrease monocyte-macrophage proatherogenic activity, and improve

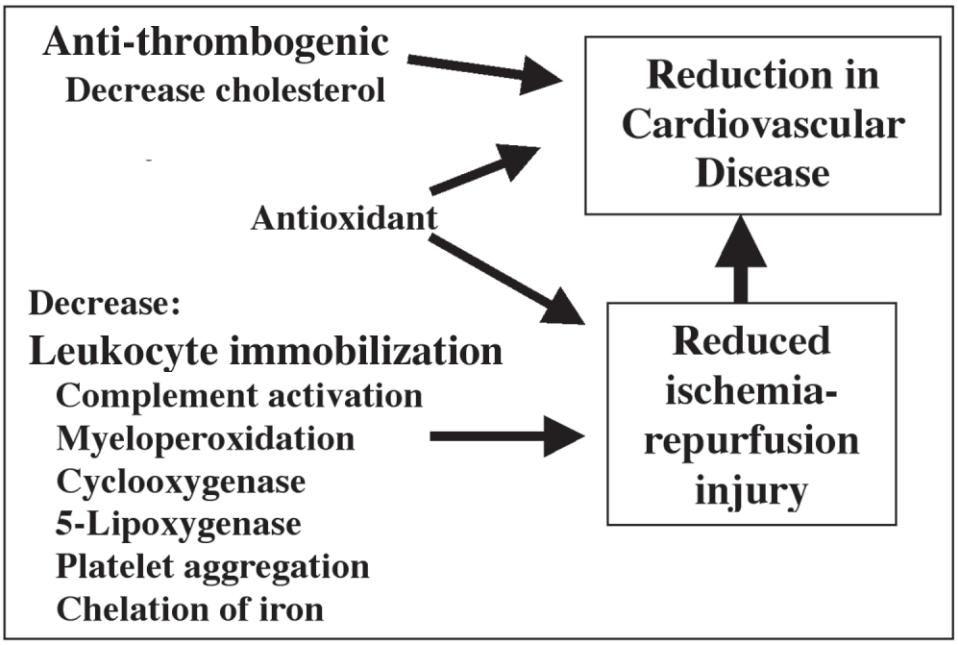


FIGURE 4. Hypothetical links between flavonoids and CVD.

endothelial function (Devaraj et al., 2002). A number of large prospective epidemiological studies were included in a meta-analysis reported by Marchioli (1999). These studies, which included a total of 84,331 patients, showed a significant inverse relationship between vitamin E intake and CVD risk, with an overall 36% reduction in relative risk of death (Marchioli, 1999). Clinical intervention trials have shown conflicting results. The preponderance of the evidence, however, shows a protective effect of vitamin E when taken at supplemental levels (200 to 800 IU) in subjects with established cardiovascular disease. These levels far exceed the average intake of the vitamin from diet alone; however, tomato products provide an average 2 to 21% of the current 22 IU recommended daily intake.

IV. EFFECTS OF PROCESSING ON BIOAVAILABILITY AND NUTRIENT CONTENT

Cooking tomatoes appears to increase the absorption of lycopene into body tissues. Additionally, many of the processed products are concentrated, and therefore also concentrating the nutrient content. Homogenization and heat treatment of tomatoes led to increased lycopene levels in plasma- and triglyceride-rich lipoprotein after 4 days of consumption in a human study (Hof et al., 2000). Cooking may, however, reduce the content of some beneficial components, such as flavonoids, vitamin C, and vitamin E (Hayman, 1999; Abushita et al., 2000). For example, flavonoid content varied from 7.1 μg/g in fresh, 4.6 μg/g in fried, and 1.3 μg/g in boiled tomatoes (Crozier et al., 1997). Tomato paste has been shown to retain 65% of total fresh fruit flavonol content. Flavonoids present in the peel leach into the paste product during the initial heating step, prior to peel and seed removal (Muir et al., 2001).

Lycopene from processed tomato products appears to be more bio-available than from fresh tomatoes (Agarwal and Rao, 2000). Bioavailability is enhanced by:

- Release from food matrix due to processing.
- The presence of dietary lipids.
- Heat-induced isomerization from an all trans to a cis conformation.
- The presence of other carotenoids, such as β-carotene.

Dietary fat may influence the absorption and resulting plasma levels of lycopene. One human study found that a single dose of unprocessed tomato juice did not change serum lycopene levels, whereas juice boiled for 1 h in the presence of 1% corn oil caused a significant increase (Garther et al., 1997). Another study showed a significant difference in total plasma antioxidant activity (FRAP) when cooking tomatoes with different oils. Olive oil improved the FRAP, while sunflower oil did not. There was also a significant increase in plasma lycopene levels with olive oil (Lee et al., 2000).

Similar differences in bioavailability are seen after the ingestion of fresh tomatoes vs. tomato paste (Garther et al., 1997). Another human study fed canned tomatoes, with varying degrees of homogenization and heating, to 17 healthy men and women to determine differences in lipoprotein lycopene and β-carotene levels. Homogenization and heating enhanced absorption (Van Let Hof et al., 2000).

V. EFFECTS OF VARIETY AND RIPENING ON NUTRIENT CONTENT

The lycopene content of tomatoes is influenced by the variety, maturity, and the environmental conditions under which they matured. Deep red varieties can contain 5 mg of lycopene per 100 g whereas yellow varieties contain only 0.5 mg per 100 g (Shi, 2001).

Yellow tomatoes have approximately 50% less vitamin C, but twice as much folate as red tomatoes. The size of the tomato variety is important for flavonoid content due to increased skin-to-pulp ratio, with smaller cherry type tomatoes being more nutrient dense. Flavonoid content has been reported to vary widely between varieties, regardless of size (Stewart et al., 2000). Generally, processing varieties of tomatoes contain a higher level of α-tocopherol than salad tomatoes. These differences were not seen for vitamin C (Abushita et al., 2000).

During the ripening process tomatoes undergo characteristic changes, leading to increased nutritive values and consumer acceptance. Some important micronutrients such as vitamin C tend to progressively decrease when going from the first color break (yellow) to the second (pink), and third (red) (Abushita et al., 1997).

VI. POSSIBLE EFFECTS ON CARDIOVASCULAR SYSTEM

A. Antioxidant

1. Mechanisms

A primary site of dysfunction in many pathological conditions of the cardiovascular system is the vascular endothelium. The major functions of the endothelium are to maintain blood circulation and fluidity, regulate vascular tone, and modulate leukocyte and platelet adhesion, and leukocyte transmigration. These functions are essential to the hemostatic processes of cell adhesion and migration, thrombosis, and fibrinolysis. A variety of risk factors, including smoking, hyperlipidemia, hypertension, diabetes, and hyperhomocysteinemia, adversely affect endothelial function.

However, the most widely accepted theory for the genesis of atherosclerosis in the vascular endothelium proposes that oxidation of low-density lipoproteins (LDL) plays a major role. Approximately half of the fatty acid molecules in LDL particles are polyunsaturated (PUFA) and therefore susceptible to oxidation in the presence of free radicals or other reactive oxygen species. Oxidized LDL particles trigger a series of events that lead to the development of atherosclerotic lesions. Oxidized LDL attracts monocytes to the vessel wall through enhanced endothelial cell production of monocyte chemotactic protein-1 (MCP-1) and the expression of intercellular adhesion molecule (ICAM-1) and vascular cell adhesion molecule (VCAM-1) (Schwenke, 1998). One recently reported *in vitro* study, involved the incubation of human aortic endothelial cell cultures with α and β carotene, β-cryptoxanthin, lutein, and lycopene, which are all carotenoids found in tomato products. The cell surface expression of adhesion molecules and adhesion to monocytic cells were measured. Among these carotenoids, lycopene was the most effective in reducing the expression of adhesion molecules (18%) and ad-

hesion to monocytes (25%) compared with control cells (Martin et al., 2000).

Once attracted to the vessel wall, monocytes transmigrate through the endothelial cell into the intimal layer of the vessel wall where they are differentiated into macrophages. The inflammatory stimulation of the endothelium plays an integral role in the development of atherosclerosis (Brown and Hu, 2001). Inasmuch as oxidized LDL are cytotoxic to the vascular cell, lipids, and lysosomal enzymes are released into the extracellular spaces, resulting in an inflammatory response. Cytokines are released that help convert monocytes into macrophages, and the released proteolytic enzymes are believed to weaken the fibrous caps of atherosclerotic lesions, leading to rupture of the plaque (Marchioli, 1999).

Oxidized LDL are more negatively charged and therefore identified by scavenger receptors on macrophages. The scavenger receptors are not regulated by negative feedback as are the native LDL receptors, and therefore the macrophages engulf massive amounts of LDL, leading to the formation of foam cells that accumulate to make fatty streaks, the first stage of atherosclerotic lesion formation (Figure 5). Oxidized LDL also inhibit the macrophage exit from the vessel wall (Quinn et al., 1987).

Oxidized LDL can also impair normal endothelial function by inhibiting nitric oxide release. Nitric oxide is the primary compound responsible for arterial vasodilation, a key component of blood pressure control. Nitric oxide also inhibits platelet aggregation (Moncada and Higgs, 1993) and the expression of VCAM-1 (Tsao et al., 1996). Homocysteine increases oxidative stress (McDowell and Lang, 2000) and down regulates nitric oxide production (Pruefer et al., 1999). Although important for maintaining normal vessel dilation, much higher levels of nitric oxide produced by macrophages react with free radicals to produce the highly damaging peroxynitrite (Nijveldt et al., 2001). Evidence suggests that dietary factors, including antioxidant vitamins, and folic acid, play an important role in modulating endothelial function. These effects may be one potential mechanism through which they reduce the risk of cardiovascular disease (Brown and Hu, 2001).

Research relating to the antioxidant activity of carotenoids was initiated when their singlet oxygen quenching and peroxy radical properties were reported in the literature. The large number of conjugated double bonds mainly influences the quenching activity of carotenoids. Lycopene was found to be the most effective quencher in plasma,

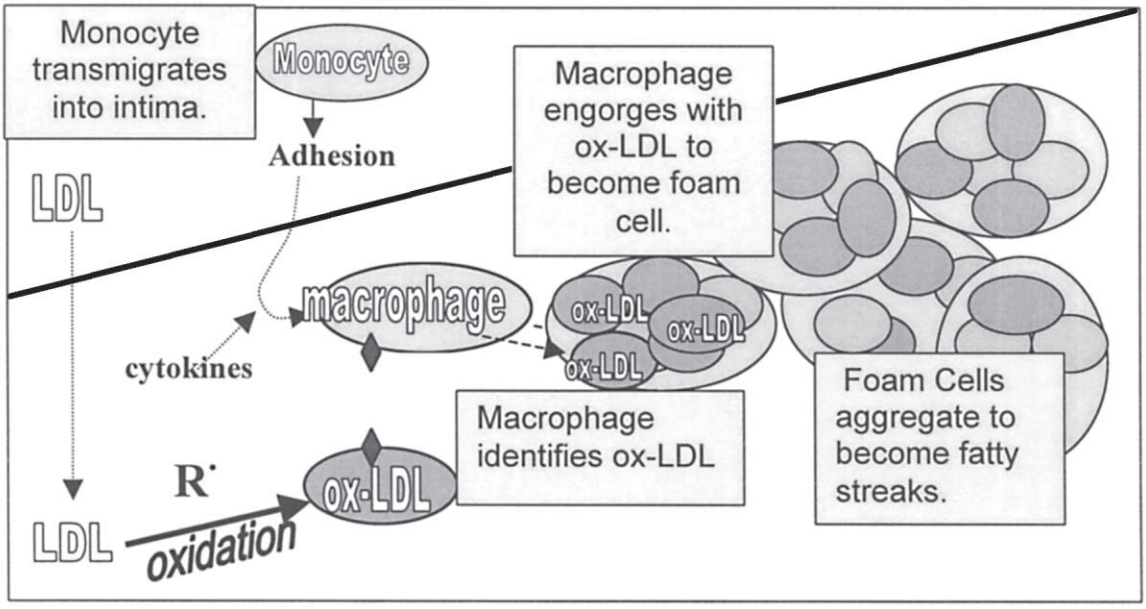


FIGURE 5. Proposed scheme of fatty streak development through LDL oxidation. The solid diagonal line represents the cell membrane. (R· free radical, ox-LDL oxidized LDL cholesterol).

LDL, and human lymphoid cells *in vitro* (Stahl and Sies, 1996).

Several endogenous and dietary antioxidants are known to function *in vivo* to prevent the oxidation of LDL. The major antioxidant credited with preventing LDL oxidation is vitamin E. However, the antioxidant environment or oxidation status of the area in which the LDL reside may influence how effectively vitamin E functions to protect LDL. Lycopene and other carotenoids may be in a position to supplement the beneficial effects of vitamin E because they tend to concentrate in low-density and very-low-density lipoprotein fractions of the serum due to their lipophilic nature. Vitamin C and flavonoids may function at the interface of the cell membrane in concert with vitamin E to protect the lipid membrane (Packer et al., 2001; Terao and Piskala, 1998).

In vitro oxidation of low-density lipoproteins showed a significant reduction with more than additive effects when lycopene (5 μmol/l) is combined with α-tocopherol (1 to 10 μmol/l). The relevance of this finding *in vivo* was confirmed when four healthy subjects were fed a fatty meal containing 30 mg lycopene in a tomato oleoresin that also contained vitamin E and flavonoids. Plasma susceptibility to oxidation was significantly reduced by 21% ($p<0.01$). The authors concluded that lycopene acted synergistically as an effective LDL antioxidant with several naturally occurring antioxidants, such as vitamin E, the flavonoid glabridin, the polyphenolics, rosmarinic acid and carnosic acid, and garlic (Fuhrman et al., 2000).

2. Epidemiological Evidence

Epidemiological studies showed that various antioxidants were associated with a lower morbidity and mortality from heart disease. The **W**orld **H**ealth **O**rganization/**Moni**tor Trends in **Ca**rdiovascular Diseases (WHO/MONICA) Study (Gey et al., 1991) reported some of the first supportive evidence of the antioxidant hypothesis for the prevention of cardiovascular disease. In this cross-cultural study involving 16 countries, both the blood levels of α-tocopherol and the tocopherol/cholesterol ratio inversely correlated with mortality rates, but vitamin C and β–carotene were not found to be protective.

Another study, reported in 1994, investigated the reasons for lowered cardiovascular death rates in Naples, Italy, compared to Bristol, England. All indicators of plasma lipid peroxidation were lower in the Naples group. After controlling for various dietary and classic risk factors, the authors concluded that the intake of tomatoes and olive oil in the Naples group might account for the differences (Parfitt et al., 1994).

The Health Professionals Follow-up Study, a prospective investigation of 50,000 males, observed lowered risk of heart disease among men with higher intakes of vitamin E but no significant reduction with vitamin C or β-carotene. Those men who had supplemented their diets with 100 IU of vitamin E for at least 2 years had a 30% reduced risk of coronary events (Rimm et al., 1993). Among men with established heart disease, they found a reduction in cardiovascular mortality with higher intake of flavonoids (Rimm et al., 1996).

The Nurses Health Study involved over 87,000 women, aged 34 to 59, with no history of cardiovascular disease. Those with a high intake of vitamin E showed a 24% reduced risk of cardiovascular events. Those who supplemented their diets with vitamin E for more than 2 years had 41% fewer coronary deaths (Stampfer et al., 1996).

Hertog and co-workers reported a strong inverse association between the intake of flavonoids and cardiovascular deaths in the Zutphen Elderly Study of men who had a history of myocardial infarction (Hertog et al., 1993). In the Seven Countries Study a significant inverse association between estimated average flavonoid intake and risk for cardiovascular death was shown during the 25-year follow-up period. It was estimated the flavonoid intake explained approximately 8% of decreased cardiovascular mortality (Hertog, 1997).

The recently reported Kuopio Ischaemic Heart Disease Risk Factor Study involved 725 men, aged 46 to 64, who were previously free of coronary heart disease and stroke. After adjusting for age, systolic blood pressure, and blood levels of folate, beta carotene and vitamin C, men with the lowest lycopene levels had 3.3-fold higher risk of

acute coronary events or stoke compared with those with higher levels (Rissanen et al., 2001).

3. Human Intervention Trials

Randomized, double blinded, placebo-controlled human trials have given inconsistent but mostly positive indications of the protective effect of antioxidants for heart disease. The Alpha Tocopherol Beta Carotene (ATBC) Study found a significant 38% reduction in the relative risk for nonfatal coronary artery disease in smokers with previous myocardial infarction who were supplemented with 50 mg of vitamin E daily, but an increase of 11% in those supplemented with β-carotene (Rapola et al., 1997a). However, in those with no previous CVD, vitamin E supplementation had no significant effect on the first major coronary event. After 6 years, nonfatal myocardial infarctions were nonsignificantly reduced by only 1% in those supplemented with vitamin E, while those who received β-carotene were not significantly different from the placebo groups. The group supplemented with vitamin E had 8% fewer CVD deaths, while the group supplemented with β-carotene had a 2% increase (Rapola et al., 1997b). Supplementation did not significantly affect the overall incidence of mortality from stroke (Leppala et al., 2000).

The Cambridge Heart Antioxidant Study (CHOAS) reported a 47% decrease in cardiovascular related mortality and nonfatal myocardial infarction after 200 days of diet supplementation with 400 or 800 IU vitamin E (Stephens et al., 1996). However, the Heart Outcomes Prevention Evaluation (HOPE) Study and GISSI (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico) Study found no significant difference between high-risk patients receiving 400 IU and 300 IU vitamin E, respectively, and those receiving a placebo. The primary endpoints were myocardial infarction, stroke, and death from CVD (Yusuf et al., 2000; GISSI-Preventione Investigators, 1999).

The recently reported Secondary Prevention with Antioxidants of Cardiovascular disease in end-stage renal disease (SPACE) Study found significant reductions in cardiovascular endpoints when feeding 800 IU vitamin E (Boaz et al., 2000). The most recently reported clinical trial involved supplementing the diets of healthy adults with 200 to 2000 IU vitamin E daily for 8 weeks. The data did not support any effect in oxidation parameters despite increasing plasma tocopherol levels (Meagher et al., 2001).

Large-scale clinical trials have provided inconclusive results when feeding β-carotene, but little research has focused on lycopene until recently. A European study, reported in 2000, found that daily consumption of tomato juice (330 mL) for a 2-week period reduced plasma Thiobarbituric Acid Reactive Substances (TBARS) by 12% and decreased lipoprotein oxidizability by 18%, while carrot juice and spinach powder had no effect (Bub et al., 2000).

A human intervention crossover study conducted in Canada (Agarwal and Rao 1998) involved feeding tomato juice, spaghetti sauce, or tomato oleoresin to 19 healthy subjects. These tomato products were fed for 1 week, with LDL oxidation being measured at the beginning and end of each feeding period. The consumption of lycopene in these foods resulted in a twofold increase in serum lycopene levels. Serum cholesterol levels did not change, but serum lipid peroxidation and LDL oxidation were significantly decreased. They concluded that daily consumption of tomato products, providing at least 40 mg of lycopene was adequate to alter LDL oxidation. A later study, feeding tomato puree with the equivalent of 7.0 mg lycopene, reported no change in antioxidant capacity in plasma as evaluated by radical trapping antioxidant parameter assay (TRAP) (Pellegrini et al., 2000). Bohm and Bitsch showed that tomato juice consumed for 2 weeks significantly increased plasma lycopene levels but did not significantly change total plasma antioxidant activity (Bohm and Bitsch, 1999). Several studies have shown serum lycopene levels remain stable in smokers, while others have shown a decrease. These observations also led to speculation as to whether the cardioprotective effect of lycopene is due to antioxidant action (Arab and Steck, 2000).

Effects of tomato juice on carotenoid concentration and oxidative susceptibility were studied in 31 healthy female Japanese students. Increased

consumption of tomato juice, high in lycopene (45 mg) but very low in β-carotene, increased both LDL and HDL lycopene, 270% and 330%, respectively. Plasma β-carotene increased in the very-low-density lipoproteins (VLDL)/intermediate-density lipoproteins (IDL), low-density lipoproteins (LDL), and high-density lipoproteins (HDL) fractions 170%, 180%, and 200%, respectively. Multiple regression analysis showed positive correlations between lag time changes for LDL oxidation and alpha tocopherol per triglyceride in LDL (Maruyama et al., 2001).

B. Nonoxidative Effects

1. HMGCoA-Reductase

In vitro assays showed that lycopene, β-carotene, tocopherol, and ascorbic acid are potent antioxidants and because antioxidant mechanisms are likely to be involved in cardiovascular disease it is tempting to assume that the health benefits of tomatoes are due at least in part to antioxidant action. However, an *in vitro* study using macrophage cell lines found that the addition of lycopene to the cell culture decreased cholesterol synthesis by 73% and increased LDL degradation by 34%. The authors proposed this effect as secondary to the inhibition of HMGCoA-reductase (Fuhrman et al., 1997). A follow-up clinical trial found that dietary supplementation of lycopene in six males for 3 months was associated with a 14% reduction in plasma LDL cholesterol. A 3:1 ratio between lowered cholesterol and the reduction in the risk of myocardial infarction would translate to an approximately 30 to 40% reduction in the risk of myocardial infarction in persons consuming lycopene regularly (Arab and Steck, 2000).

2. Homocysteine

Homocysteine is a sulfur-containing amino acid intermediate derived from the demethylation of methionine in producing cysteine. Elevated homocysteine levels have been linked to the incidence of cardiovascular disease. Folic acid is an important methyl group exchange vitamin and therefore influences homocysteine levels. Ho-

TABLE 3
Summary of Major Case Control and Cohort Studies

Authors	Number of Subjects/ (Controls)	Lycopene Measurement	Outcome	Odds Ratio P value	Major Factors Controlled
Street et al. 1994	123/(246)	Serum	Myocardial Infarction	.75 *ns	None
Iribarren et al. 1997	231/(231)	Fasting serum	Intima-media thickness	.81 *ns	Age, chol/trig, educ. level, smoking, BMI, alcohol, HTN, Diabetes, vitamin supp use.
Kohlmeier et al. 1997	662/(717)	Adipose tissue	Myocardial Infarction	.52 P=.005	Age, center, BMI, smoking, family history of disease and HTN
Gomez-Aracena et al. 1997	100/(102)	Adipose tissue	Myocardial Infarction	.39 P=.04	Age, family history of CVD, Smoking
Klipstein-Grobusch et al. 2000	108/(109)	Serum	Aortic atherosclerosis	.55 non-smokers .35 current or former smokers	Age, sex, serum cholesterol, smoking, hip-waist ratio, alcohol intake.
Rissanen et al. 2000	520	Plasma : lower vs. higher than median.	Intima-media thickness of carotid artery wall	Men: P= .003 Women: *ns	CVD risk factors and nutrient intake.
Rissanen et al. 2001	725	Serum: lowest vs. highest quartile	Acute coronary events or stroke	P= .001	Age, systolic blood pressure, blood levels of ascorbic acid, beta carotene, and folate.

*ns= non-significant

mocysteine increases platelet aggregation and thrombosis by stimulating thromboxane synthesis and inactivating anticoagulants (Haynes, 1999). To date, there have been no studies reported on an association between tomato consumption and homocysteine levels. However, tomatoes are a dietary source of folate and inadequate plasma concentrations have been associated with elevated homocysteine levels.

3. Platelet Aggregation

When tomato extract was incubated with blood taken from healthy subjects, a 70% reduction was seen in platelet aggregation induced by collagen, adenosine diphosphate (ADP), and thrombin, the most potent agonist of platelet aggregation. The mechanism of this inhibition did not involve the cyclooxygenase system, as seen with aspirin. The modulation of platelet activity could potentially provide therapeutic benefit in preventing the pathological processes that led to CVD (Dutta-Roy et al., 2001).

VII. CONCLUSIONS

Tomatoes and tomato products contain several nutrients associated with theoretical or even proven effects related to cardiovascular disease. Overall, the strongest evidence comes from epidemiological data, linking serum levels of nutrients with decreased incidence of cardiovascular disease outcomes such as myocardial infarction, atherogenesis, and mortality. However, with these studies it is difficult to control for all confounding factors. Clinical intervention trials offer conflicting but overall positive results, with perhaps a lesser degree of confounding effects.

Fresh tomatoes are available for consumption year round. An important point is that fresh tomatoes are not only nutrient rich, but are also devoid of nutrients such as saturated fatty acids and cholesterol, considered unhealthy in terms of cardiovascular disease. Fresh tomatoes are also very low in sodium, although some processed tomato products, such as paste and tomato sauces, do contain higher levels.

Many of the nutrients found in tomatoes are proven antioxidants, some of which have been shown to work in concert with respect to improving oxidation status. The evidence of feeding individual antioxidants is conflicting, while the evidence of eating fruits and vegetables is more consistent in terms of protection from heart disease. Therefore, it would seem prudent to identify and consume foods, such as tomatoes, which provide a combination of these antioxidants as a source of cardiovascular protection (Table 4).

With this review of the scientific literature, we are proposing that tomatoes, and products derived from them, should be included as cardiovascular protective foods. The data are compelling and the beneficial health effects will continue to be defined as more research is accomplished in this area.

TABLE 4
Contribution of Tomato Serving to Average Need or Intake

Nutrient, unit	RDA	Average Daily Intake	Amount per serving			
			Range	Average	Average % of RDA	Average % of Intake
Vitamin E, IU	22	-	.22 – 3.13	1.37	**6.2**	-
Vitamin C,mg	*90/75	-	2.6-66.4	20	***22/27**	-
Folate, µg	400	-	2.6-27	13	**3.2**	-
Flavonoids, mg	n/a	21.3	n/a	2.3**	n/a	**10.8**
Lycopene, mg	n/a	25	2.7-20.8	12.6	n/a	**50.4**

RDA not established for flavonoids and lycopene *men/women ** Value from fresh tomato only

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