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Lycopene and human health-A review

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ABSTRACT

Functional and nutraceutical foods have shared the disease load of huge population. This has led to the consumption of plant-based phytonutrients act as preventives agents when taken as dietary supplements. Their health promoting potentials are due to presence of functional ingredients. The antioxidant properties of lycopene are thought to be primarily responsible for its beneficial properties. Lycopene bioavailability, tissue distribution, metabolism, excretion, and biological actions in humans are beginning to accumulate although much additional research is necessary. Lycopene is an important carotenoids.These are found to be very beneficial for maintaining a good health and helps in preventing cancer, cardiovascular and other diseases.

Key words : Anticancer, Antioxidant, Cardiovascular diseases, Lycopene, Phytochemical.

Epidemiological evidences link diet rich in fresh fruits and vegetable to protection against chronic degenerative diseases (Cox *et al*. 2000). Fruits and vegetables are gaining immense importance in the domain of nutrition owing to presence of vital phytochemicals and bioactive molecules. Their health promoting potentials are due to presence of functional ingredients, e.g., polyphenols, ûavonoids, tannins, anthocyanins, etc. (Butt *et al*.2008). These compounds trigger and alter body metabolism and modulate detoxiûcation mechanism. Thereby, provide protection against lifestyle disorders, cancer insurgence,etc. Nevertheless, antioxidant potential of fruits and vegetables varies thus their balanced consumption is better than reliance on few speciûc groups Manach *et al*. (2004). Plant based diet contains several bioactive ingredients with vital role to perform various metabolic functions like growth, development and protective mechanism against physiological threats. In this context, functional and nutraceutical foods have shared the disease load of huge population .The plants that are rich sources of bioactive molecules include garlic, ginger, tea, ginseng, black cumin, mulberry, raspberry etc. (Butt *et al*.2009). This has led to the consumption of plant-based phytonutrients as preventives agents as dietary supplements. These are similar in appearance to conventional foods and used in normal diet but have advantages of aiding physiological functions. In essence, combination of functional foods and healthy life style has a positive contribution to health and well-being.

Tomatoes are an integral part of diet worldwide, accounting lycopene in American diet, and also important component of the Mediterranean diet. Studies have established a link between dietary intake of tomatoes having carotenoid and lycopene compounds that can reduce risk of various diseases, like cancer and cardiovascular diseases. Lycopene is the red carotenoid pigment found predominantly in fruits and vegetables, most especially in tomato species (Basu and Imrhan, 2007). More recently lycopene, a member of the carotenoid family of compounds has attracted the greatest interest among the carotenoids from the medical research (Levy *et al*.2004). Lycopene is also a major carotenoid in human blood found to have comparatively, stronger antioxidant properties than major plasma carotenoids (Cho *et al*. 2004). Lycopene is reported to be a highly effective antioxidant owing to its ability to act as a free radical scavenger and has the highest singlet oxygen quenching rate of all the carotenoids tested from biological systems (Rao and Rao, 2007).

LYCOPENE SOURCES AND INTAKE

Lycopene is a fat-soluble pigment that gives tomatoes and a limited number of other foods their red color. More than 80% of dietary lycopene intake in the U.S. is derived from processed tomato products such as ketchup, tomato juice, spaghetti sauce, and pizza sauce (Clinton, 1998).Tomatoes are also rich in folate and potassium, and there is almost 3 times as much vitamin C as lycopene in a tomato. Thus, in studies of health benefits of tomatoes, one

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must consider that they are also rich in nutrients other than lycopene. The amount of lycopene present in processed foods is often much higher than that found in fresh foods given that processing often involves concentration via water loss.

Table 1 represents lycopene content in the food .Tomatoes and tomato-based products are the major and the best sources of lycopene in the human diet. Lycopene present in fresh tomatoes consists predominantly of all-translycopene (Zofia, 2006). Happily, cooking doesn't destroy lycopene, so pizza sauce is just as good as a fresh tomato. In one study, however, when heated tomato juice mixed with oil was consumed, serum concentrations of lycopene increased, with a peak 24–48 h after ingestion (Stahl W and Sies H,1996)

There is no consensus on recommended daily dose of lycopene since carotenoids are considered to be nonessential micronutrients Dietary intake of lycopene varies greatly depending upon the studied population. The average Italian consumes 14.3 mg/day of total carotenoids. Lycopene makes up the largest proportion of carotenoids in the Italian diet, with an average intake of 7.4 mg/day (Lucarini *et al*. 2006). The average daily intake of lycopene in the United States ranges from 6.6–10.5 mg/day for men and from 5.7–10.4 mg/day for women ,1.1 mg/day in the United Kingdom, 3.8 mg/day in Australia, where as in the industrialized European countries, daily intake of lycopene varies from 0.7mg (Finland) to 1.3mg (Germany) (Porrini and Riso,2005). Higher intake of lycopene at daily dosage up to 100 mg has no side effects in volunteers (Shao and Hathcock, 2006). Clinical studies use moderate amounts of lycopene rarely exceeding 10 mg per day.

LYCOPENE BIOAVAILABILITY, ABSORPTION AND DISTRIBUTION

Lycopene bioavailability can be affected by a number of factors, including food processing and dietary composition. Lycopene can occur in several forms in fresh plant foods, including carotenoid-protein complexes in chloroplasts or in crystalline form inside chromoplasts (Parada and Aguilera, 2007). Chloroplasts have high resistance to gastric and intestinal digestion (Schweiggert *et al*. 2014).Thus,food matrix structure predetermines significantly the bioavailability of lycopene. The effects of processing and storage on lycopene structure and stability are of interest for a number of reasons. Improper processing and storage (i.e., exposure to light and oxygen) may alter the ratio of lycopene isomers or degrade lycopene entirely, making these food products less desirable to the consumer (Xianquan *et al*. 2005). In fact, thermal processing generally improves lycopene bioavailability by disrupting cellular membranes, which allows lycopene to be released from the tissue matrix (Nguyen *et al*. 2001).

Table 1: Lycopene content of Tomato foods

Food	Lycopene content (mg/100 g
Tomatoes, raw	0.9–4.2
Tomatoes, cooked	3.7–4.4
Tomato sauce	7.3–18.0
Tomato paste	5.4–55.5
Tomato soup (condensed)	8.0–10.9
Tomato juice	5.0–11.6

Source : Shi and Le Maguer (2000)

Once ingested, lycopene must first be released from the food matrix before it is incorporated into mixed micelles. Micelles contain bile salts, cholesterol, and fatty acids from the meal, and the amphiphilic nature of the micelle structure helps to keep the lipophilic nutrients soluble in the aqueous digesta. The micelles approach the unstirred water layer of the apical side of the intestinal cells (enterocytes), and lycopene passively diffuses across the apical membrane (During and Harrison, 2004). Lycopene was absorbed by the same route as dietary lipids, i.e., passive diffusion (Furr and Clark, 1997).Once inside the enterocyte, lycopene is packaged with other dietary lipids into chylomicrons (During and Harrison, 2004). Chylomicrons are then transported across the basolateral membrane and make their way into the lymphatic system, which eventually releases chylomicrons into the blood.

One post-prandial human study demonstrated that co-consumption of tomato puree (30 mg lycopene) + spinach lutein (30 mg) or encapsulated lutein (30 mg) reduced chylomicron lycopene levels by 70% and 61% respectively, as compared with lycopene levels observed after consumption of tomato puree alone . However, when subjects consumed these foods daily for three weeks at half of the previous dose (15 mg of lycopene + 15 mg lutein), no difference was observed in steady-state plasma levels of lycopene (Tyssandier *et al*. 2002). A human study by Johnson *et al*. (1997) observed that co-administration of β-carotene crystals in oil (60 mg) with lycopene crystals in oil (60 mg) increased the 24-hour postprandial serum area under the curve (AUC) of lycopene by four-fold as compared with the administration of lycopene alone.

In addition, lycopene absorption may be affected by other factors such as probiotics and single nucleotide polymorphisms (SNPs). Consumption of a probiotic-containing yogurt versus a regular yogurt lowered blood lycopene levels in a group of 17 women who consumed probiotics for a total of 4 weeks. This study suggests that probiotics may affect lycopene bioavailability or metabolism (Fabian and Emaldfa, 2007).

Lycopene distribution among tissues is very selective. The absorbed lycopene is distributed throughout the body via circulatory system. It is the most predominant carotenoid in human plasma with half life of about 2-3 days (Stahl and Sies, 1996). The concentrations were within the range of 0.2– 21.4 nmol/g tissue. Plasma lipoproteins are major delivery vehicles of carotenoids and lycopene in the human body (Dias *et al*. 2014). Therefore,it is very likely that the

differences in lycopene tissue levels are related to variation in tissue expression of lipoprotein receptors and cholesterol transporters. Lycopene concentration as shown in Table 2 was highest in human testes, followed by adrenal gland > liver > prostate > breast > pancreas > skin > colon > ovary > lung > stomach >kidney > fat tissue > cervix (Goralczyk and Siler, 2004). The excretion of lycopene through feces and urine was also reported. In human, total serum carotenoids is about 1–2 μM, with lycopene being one of the major carotenoids present in human serum(Su *et al*. 2002).The level of plasma lycopene can vary among the people from different countries.

LYCOPENE-RICH BY-PRODUCTS FROM FOOD PROCESSING

Food processing by-products from the tomato puree and sauce industry are commonly used in the development of lycopene-rich products. Tomato skins contained a high amount of lycopene. Among the agro-industrial byproducts (cereal and pulsed, distillery, oil-seeds, sugar industry, textile industry, vegetables and fruits industry, vegetables crop, and miscellancous), tomato wastes are the only by-products that are rich in lycopene (Krishna, 1985).Fortification with lycopene in dry fermented sausage was also done by adding dried tomato peel to the meat mixture during the sausage production (Calvo *et al*. 2008). The development products with extrusion processing using barley-tomato pomace blends and processing into snacks (Altan *et al*. 2008). Besides, enrichment of low quality edible oils such as refined olive oil, extra virgin olive oil and refined sunflower oil by lycopene from tomato peels or tomato puree was proven to induce thermal stability to these edible oils (Benakmoum *et al*. 2008). The idea of using lycopene-rich by-products from tomato peel and seed for hen feed will further enrich the egg yolk with lycopene. However, only low amounts of lycopene were found to be transferred to the egg yolk (0.1% from tomato peels and 0.7% from tomato seeds (Knoblich *et al*. 2005).

EFFECT OF PROCESSING ON LYCOPENE

Table 2: Lycopene levels in Human tissues

Tissue	Lycopene (nmol/g wet weight
Adipose	0.2-1.3
Skin	0.4
Brainstem	Not detectable
Liver	1.3-5.7
Lungs	0.2-0.6
Adrenal	1.9-21.6
Stomach	0.2
Colon	0.3
Breast	0.8
Testis	4.3-21.4
Ovary	0.3
Prostate	0.8

Source: Clinton *et al*. 1996

The quality of lycopene-rich by-products after food processing such as blanching and drying, where blanching in hot water at 75°C for 2 min could help to reduce the drying time and increase the lycopene bioavailability (Dhas *et al*. 2004). Heat processing increases the lycopene bioavailability of lycopene by breaking cell walls and allowing extraction of lycopene from the chloroplasts,where it is found in raw tomatoes (Stahl and Sies,1996). There is an overall increase of antioxidant potential by heating tomato juice due to the formation of melanoidins during the advanced steps of the maillard reaction (Anese *et al*. 1999).

ANTIOXIDANT EFFECT OF LYCOPENE

Lycopene is the most potent antioxidant among pigments (e.g. from the most potent to the least potent antioxidants are: lycopene, α-tocopherol, α-carotene, β-cryptoxanthin, zeaxanthin=β-carotene, and lutein).Biological activities of lycopene are antioxidant activity (singlet oxygen quenching and peroxyl radical scavenging), induction of cell-cell communication, and growth control, but no provitamin A activity (Stahl and Sies., 1996). The synergistic antioxidant activity of lycopene in combination with α-carotene, vitamin E, and lutein. Their synergistic interactions, when used in combination, may be responsible for the observed beneficial effects of tomato-based products.Mixtures of lycopene and vitamin E appear to have the greatest synergistic antioxidant activity (Shi *et al*. 2004). Indeed, lycopene had the strongest singlet oxygen-quenching capacity of several carotenoids, with α-carotene, β-carotene, and lutein next in capacity. The weakest singlet oxygen quencher of the antioxidants studied was α-tocopherol, which is found in much greater concentrations in many body systems (Lenore and Susan, 2000). Lycopene is effective in protecting blood lymphocytes from NO_2 radical damage.DNA damage is a useful biomarker of the oxidative status and the antioxidant defense system.

HEALTH BENEFITS OF LYCOPENE

Over the past decade, the effects of lycopene have been studied with respect to a wide range of diseases like various cancers, CVD etc. (Dahan *et al*. 2008, Riccioni *et al*. 2008).

Lycopene and cancer: Cancer can have profound social and economic consequences for people in India.Slightly more than 1 million new cases of cancer are diagnosed every year in a population of 1·2 billion. However, an estimated 600 000–700 000 deaths in India were caused by cancer in 2012 (Mallath *et al*. 2014). The consumption of tomatoes and tomato products has been associated with a reduced incidence of a number of different types of cancers, most notably prostate, lung, and stomach (Giovannucci, 1999). lycopene is more potent than α and ß-carotene in inhibiting the cell growth of various human cancer cell lines (levy *et al*. 1995). Lycopene had anticarcinogenic activities in mammary gland, liver, skin and lung. Lycopene has also shown promise for leukoplakia, a precancerous condition

of the mouth and other mucous membranes. In a double-blind, placebo-controlled study, 58 people with oral leukoplakia received either 8 mg oral lycopene daily, 4 mg daily, or placebo capsules for three months (Singh *et al*., 2004). Participants were then followed for an additional two months. The results indicated that lycopene in either dose was more effective than placebo for reducing signs and symptoms of leukoplakia, and that 8 mg daily was more effective than 4 mg.

Prostate cancer: Prostate cancer is the most common malignancy and cause of death in men. Although genetic factors and age are important determinants of the risk, environmental exposures, including diet are increasingly being associated with the disease. A pilot study suggests that a tomato extract containing lycopene and other tomato carotenoids and phytochemicals may have a potential role in the treatment of prostate cancer (Omer *et al*. 2000). Consumption of lycopene, a carotenoid without provitamin A activity, has been associated with a lower risk of prostate and breast cancer (Gunasekera *et al*. 2007). Increasing evidence suggests that a single serving of tomatoes or tomato products ingested daily may contribute to protect from DNA damage. As DNA damage seems to be involved in the pathogenesis of prostate cancer, the regular ingestion of tomatoes or tomato products might prevent the disease (Ellinger *et al*. 2006). In one study by Chen *et al*. (2001), 32 prostate cancer patients consumed tomato sauce daily for three weeks (30 mg lycopene/day) before a radical prostatectomy.

Lycopene and ageing: Plasma lycopene level can become significantly reduced during the process of ageing. Older individuals show statistically lower lycopene concentration values in blood as compared to younger matching individuals with similar ethnic and dietary background (Semba *et al*. 2010). Intestinal absorption of carotenoids is a complex multistage process which requiresa fully intact and functioning gastrointestinal epithelium and subset of various enzymes (Davidsson and Haskell, 2011). Acute and chronic gastritis and abnormal gastric acid secretion as well as deviations in intestinal enzyme spectrum during ageing are considered to be major causes of reduced intestinal carotenoid absorption in older individuals (Akhtar *et al*. 2013). Moreover, depleted levels of lycopene and other carotenoids in older individuals are believed to reflect age-related changes in the intestinal microbiota, which regulates bioavailability of carotenoids and polyphenols in the large intestine (Bohn, 2014). Although additional research to explain the causes and mechanisms of lycopene deficiency in ageing is required, it is clear now that correction of carotenoid deficiency in older individuals may have anenormous impact on their health status. Moreover, lycopene has to suppress activation of them TOR/AMPK cascade,a major metabolic pathway linked to ageing (Menendez *et al*. 2013).There are numerous pieces of clinical evidence suggesting that lycopene supplementation prevents osteoporosis and incidence of bone fractures (Sacco *et al*. 2013), improves pulmonary function (Samba *et al*. 2012), delays skin ageing (Schagen *et al*. 2012), and enhances physical performance in elderly patients (Alipanah *et al*. 2009).The set of clinical consequences of lycopene deficiency is greatly enlightened by the solid body of clinical evidence revealing the crucial role of lycopene in maintaining prostate health and its ability to prevent prostate cancer in elderly males(Mariani *et al*. 2014).

Oxidative stress: The process of oxidation is essential invitality of life coupled with production of ROS. A natural balance between ROS production and antioxidant defense system exist and its imbalance results in oxidative stress resulting in damage to membranes and cell constituents such as DNA, lipids, and proteins (Fig 1). The intake of antioxidant rich diets or supplementation with bioactive molecules, like vitamins, carotenoids, and tannins may provide protection against oxidative damage (Gu *et al*. 2008). Lycopene has antioxidative perspectives, which can prevent DNA damage and hence protect against mutations that cause cells cancer development (Lindshield *et al*., 2007). Lycopene may also modify molecular biomarkers of atherosclerosis (Badimon *et al*. 2010).

Lycopene and cardiovascular disease: Cardiovascular diseases (CVDs) have now become the leading cause of mortality in India. Ischemic heart disease and stroke are the predominant causes and are responsible for >80% of CVD deaths (Prabhakaran *et al*. 2016). Tobacco use, unhealthy diet, physical inactivity and high intake of alcohol increase the risk of CVD. Increase in LDL oxidation is hypothesized to be causally associated with increasing risk of atherosclerosis and coronary heart disease. Cumulative evidences in literature support the role of lycopene in the prevention of cardiovascular diseases (CVD). Increased plasma lycopene levels have been associated with reductions in CVD risk and have also been reported to improve

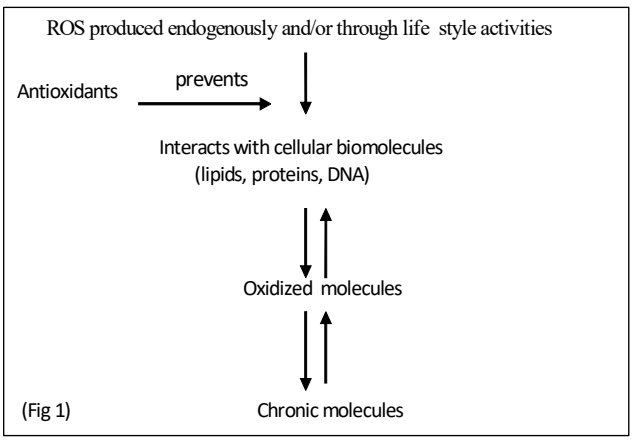

Fig-1: Oxidative stress

biomarkers associated with CVD. A study by Sesso *et al* (2003) of 38,445 women found that higher levels of tomato-based product intake were associated with a reduced risk of cardiovascular disease and myocardial infarction.

Lycopene may reduce cholesterol synthesis and increase low-density lipoprotein (LDL) degradation (Arab and Steck, 2000). A randomized crossover study by Agarwal and Rao (1998) used four different treatments: placebo (0 mg lycopene), tomato juice (50.4 mg lycopene), spaghetti sauce (39.2 mg lycopene), and tomato oleoresin (75 mg lycopene). Nineteen healthy subjects consumed each treatment daily for one week and went through a one-week washout period between each treatment week. Serum lycopene concentration doubled in subjects on the lycopene-containing treatments. In addition, a significant decrease in serum lipid peroxidation and LDL oxidation was observed after subjects consumed any one of the three lycopene-containing treatments. Shen *et al.* (2007) treated 24 subjects with either fresh tomato, tomato juice, or a lycopene drink (all delivering 40 mg lycopene/day) for six weeks. This study found that triglyceride levels and LDL cholesterol were decreased, and high-density lipoprotein (HDL) cholesterol increased in subjects who consumed fresh tomato and tomato juice. In a more recent study, 18 healthy men and women consumed a soy-tomato beverage daily (21 mg lycopene/ day) for eight weeks (Bohn *et al* 2009).

Other diseases: Although studies on the ability of lycopene to modify cancer and CVD risk are most prevalent, there have been numerous other diseases that have also been investigated in relation to lycopene consumption. These conditions include hypertension, (UV)-induced sunburn, gingivitis, mental disorders, and asthma.

Hypertension, a 'silent killer,' is a disorder in which symptoms are not observed until a more advanced and a fatal stage is reached. The antioxidant property of lycopene has attracted scientific research into its protective role in hypertension. A recent study showed lycopene supplementation of 15 mg/ day for 8 weeks significantly decreased systolic blood pressures from baseline values to 144 mm Hg to 134 mm Hg in mildly hypertensive subjects (Paran, 2006). In another study a significant reduction in plasma lycopene was observed in the hypertensive patients compared to normal subjects. Recognizing the importance of antioxidants in the management of hypertension a 'dietary approach to control hypertension (DASH)' diet is recommended that contains substantially higher levels of lycopene along with other carotenoids, polyphenols, flavanols, flavanones and flavan-3-ols (Most, 2004).

The ability of lycopene to affect was investigated in 36 healthy adults, whereby subjects consumed synthetic lycopene alone, a soft-gel encapsulated tomato extract, or a tomato drink for 12 weeks. Dorsal skin was irradiated at weeks 0, 4, and 12 with artificial UV light at levels high enough to cause mild sunburn. The subjects consuming the tomato extract and tomato drink had a 38% and 48% decrease, respectively, in solar simulator–induced sunburn at week 12, compared with only a 25% decrease in the group treated with synthetic lycopene (Aust *et al*. 2005).

A randomized, placebo-controlled, split-mouth study of gingivitis was performed by Chandra *et al*. (2007) in 20 healthy subjects with clinical signs of gingivitis. The treatment group (n = 10) was supplemented with 8 mg/day lycopene, whereas the control group (n = 10) received a placebo daily for two weeks. In this study, patients receiving the lycopene treatment showed statistically significant reductions in gingivitis and bleeding index.

Brain is a vulnerable organ for oxidative damage due to high levels of oxygen uptake and utilization, high lipid content and low antioxidant capacity. Rao and Balachandran (2003) suggested the role of lycopene in neurodegenerative diseases including Alzeheimers disease. Lycopene was shown to cross the blood brain barrier and be present in central nervous system (CNS) in low concentration. Significant reduction in the levels of lycopene was reported in patients suffering from Parkinson's disease and vascular dementia (Foy *et al*. 1999). Likewise, Suganuma *et al*. (2002) reported that tomato ingestion might serve as a preventive therapy against neurodegenerative diseases such as Parkinson's disease caused by 1-methyl4-phenyl-1, and other environmental toxins. Moreover, it was also suggested to provide protection against amyotrophic lateral sclerosis disorder in humans (Longnecker *et al*. 2000).

Research has also suggested that lycopene have a therapeutic effect on asthma. A randomized, crossover study of 17 asthmatic adults treated with placebo, tomato extract, 45 mg/day lycopene), and tomato juice (45 mg/day of lycopene) for seven days showed a reduced airway neutrophil influx and a reduced sputum neutrophil elastase activity after the tomato extract and tomato juice treatment (Wood *et al*. 2008). During placebo treatment, plasma lycopene concentration decreased, percent neutrophils increased, and neutrophil elastase levels increased. This study suggests that intake of lycopene may improve lung function in asthmatics.

It is reported that persons with a high intake of carotene reduce the incidence of risk of cataract (Cumming *et al*. 2000) and the relationship between nuclear cataract and intakes of α carotene, β-carotene, lutein, lycopene and cryptoxanthin stratifying by gender and by regular multivitamin use . It has been reported that lycopene prevents cataractogenesis *in vivo* and *in vitro* by virtue of its antioxidant properties (Gupta *et al*. 2003). It was also found that lycopene prevented sugar-induced diabetic cataract (Mohantay *et al*. 2002).

CONCLUSION

Fruits and vegetables are gaining immense importance in the domain of nutrition owing to presence of vital phytochemicals and bioactive molecules. These compounds trigger and alter body metabolism and modulate detoxiûcation mechanism. Lycopene is naturally occurring substances found in tomatoes. Lycopene have possible benefits against diseases, among other health issues. Lycopene is considered as antioxidant and anticancer agents. Thereby, it provide protection against lifestyle disorders and cancer insurgence. Moderate amounts of whole food-based supplementation (2–4 servings) of tomato soup, tomato puree, tomato paste, tomato juice, or other tomato beverages, consumed with dietary fats, such as olive oil or avocados, leads to increases in plasma carotenoids, particularly lycopene. These foods may have both chemopreventive as well as Cardiovascular diseases. A combination of naturally occurring carotenoids, including lycopene, in food sources and supplements, is a better approach to disease prevention and therapy, versus a single nutrient. The conclusion may be drawn that consumption of naturally occurring carotenoid-rich fruits and vegetables, particularly processed tomato products containing lycopene, should be encouraged, with positive implications in health and disease.

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