



## Antioxidant and nutraceutical potential of tomato for health and life quality: A review

Muhammad Suhail Ibrahim<sup>a\*</sup>, Ahmed Mujtaba<sup>b</sup>, Ishtiaq Hassan, Wajahat Azeem<sup>d</sup>, Muhammad Waqar<sup>e</sup>, Itrat Fatima, Muhammad Nadeem<sup>g</sup>, Asma Sohail<sup>a</sup>, Kashif Sarfraz Abbasi<sup>a</sup>, Abdus Samee<sup>a</sup>

a. Institute of Food and Nutritional Sciences, PMAS-Arid Agriculture University, Rawalpindi, Pakistan 46000

b. Department of Food Science and Technology, Hamdard University, Islamabad, Pakistan

c. Government of the Punjab Agriculture Department, Lahore, Pakistan

d. Department of Plant Pathology, PMAS-Arid Agriculture University Rawalpindi, Pakistan 46000

e. Department of Food Science and Technology, Hamdard University, Islamabad

f. Institute of Food Science & Nutrition, University of Sargodha, Sargodha, Pakistan

g. Department of Entomology, PMAS-Arid Agriculture University, Rawalpindi, Pakistan 46000

**Abstract:** The significance of diet in connection to human health has raised consumer demand for foods high in nutraceuticals, particularly fruits and vegetables. The antioxidant phytochemicals vitamins A, C, & E, beta-carotene, carotenes, flavonoids, flavones, total phenolic compounds, etc., are just a few of the many antioxidant phytochemicals that tomatoes are a rich source of. DNA, protein, and lipid are all severely harmed by oxidant byproducts of normal metabolism. This damage is a potential contributor to aging as well as degenerative and malignant disorders such as cataracts, immune system decline, cardiovascular disease, and a variety of cancers. Flavonoids, ascorbate, tocopherol, and carotenoids, among others, are antioxidant defenses against these harms. The phenolic chemicals found in tomatoes may also function as antimicrobials, aiding in the management of a wide range of infections. Finally, we want to underline how important it is to establish a connection between the unique breeding of tomato plants and genetic research with the production and overexpression of compounds that are beneficial to human health.

**Keywords:** Antioxidant activity, Bioavailability, Healthy life, phenolics, therapeutic effect.

### 1. Introduction

Current recommendations to cope with malignant and chronic disorders recommend increased intake of a nutraceutical-rich diet ([Chang et al., 2006](#)) including fruits and vegetables ([Santos-Cervantes et al., 2007](#); [Vrieling et al., 2009](#)). The bioactive compounds in fruits and vegetables are responsible for human health by increasing in body's defense system; hence promoting life quality ([Pila et al., 2010](#); [Timlin & Pereira, 2007](#)). Tomato (*Lycopersicon esculentum* Mill.) is a potential component of a healthy diet because it not only contains nutritional antioxidants such as vitamins A, C, and E, but also a range of non-nutritional antioxidants, such as beta-carotene, carotenoids, flavonoids, flavones, and total phenolic compounds ([Javanmardi & Kubota, 2006](#); [Soto-Zamora et al., 2005](#)). The antioxidant potential of tomatoes is thought to be closely related to their functional quality ([Tyssandier et al., 2004](#)). The beta-carotene, lycopene, found in tomatoes, play a defensive role ([Oshima et al., 1996](#)), as well as ascorbic acid ([Lee & Kader, 2000](#)), total phenolic compounds, and other vitamins ([Abushita et al., 1997](#)), and minerals play the same role. These carotenoids and ascorbic acid are crucial in preventing reactions caused by reactive oxygen species ([Lee & Kader, 2000](#); [Leong & Shui, 2002](#)). The antioxidant properties of tomatoes prevent and postpone the oxidative reactions that result in degenerative illnesses, both individually and collectively ([Block et al., 1992](#)). Numerous investigations have demonstrated the potency of these as oxygen quenchers and oxygen scavengers ([Giovanelli et al., 1999](#)). Electron donation and cation production are both part of the mechanism of action. While radical adduct production is a scavenger feature. The cation radicals and their radical adduct are stable and decompose in a gradual bimolecular manner ([Miller et al., 1996](#)). Tomato availability and total antioxidants may be influenced by biotic and abiotic factors.

[Received] 09 Apr 2023; Accepted 21 June 2023; Published (online) 22 June 2023]

Finesse Publishing stays neutral regard to jurisdictional claims published maps



Attribution 4.0 International (CC BY 4.0)

Corresponding email: [Chaudhary.muhammad@hotmail.com](mailto:Chaudhary.muhammad@hotmail.com) (Dr Muhammad Suhail Ibrahim)

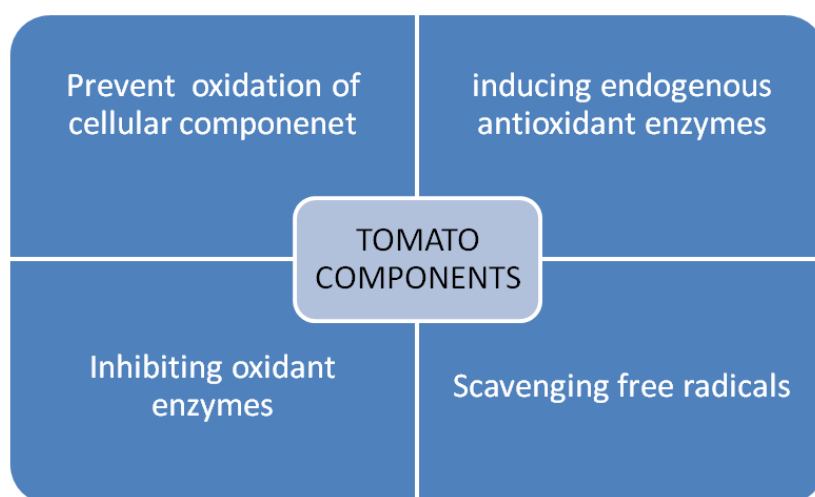
DOI: 10.61363/fsamr.v2i1.58

Improving one's knowledge of the availability of functional components is key to understanding the possible mechanisms that affect human health and describing the impact that tomatoes have on healthy living ([Lafay & Gil-Izquierdo, 2008](#); [Zhao & Moghadasian, 2008](#)).

This paper provides a summary of the information on tomato fruit's antioxidant capability. Additionally, the significance and biological functions of the antioxidant component in improving human health are discussed. The review also gives a pinched view of dietary intake and pharmacokinetic properties of the functional components present in tomatoes.

## 2. Antioxidant Components in Tomato

Tomatoes are a rich source of nutritive antioxidants like vitamins A, C, and E, and non-nutritive antioxidants like beta-carotene, flavonoids, flavones, total phenolic compounds, etc. In addition to proximate composition, the fruit also contains other valuable phytochemicals that include carotenoids and polyphenols ([Tonucci et al., 1995](#)). For instance, carotenoids contain a red pigment, lycopene, phytofluene, and phytoene. Flavonol content is also high in fruit skin, conjugated in the forms of quercetin and kaempferol, up to 98% ([Stewart et al., 2000](#)). Various research studies emphasize the functional compounds in fruits and vegetables for human health. The Organizations working on human health emphasize the importance of antioxidant activity for curing diseases like cardiovascular diseases, diabetes, cancer, and obesity ([Organization, 2002](#); [Stapleton et al., 2008](#)). Most compounds, especially antioxidants in tomatoes, are responsible for curing disease. The antioxidant property of fruit varies greatly due to the enormous variety of species, stages of ripeness, years of growth, climatic conditions, light, temperature, soil, fertilizer, irrigation, and other cultivation, handling, and storage conditions ([YILMAZ, 2001](#)).



**Figure 1.** Property supporting the health-beneficial effect of tomatoes.

Tomatoes and food products that contain tomatoes make it easier for the body to absorb a range of carotenoids, including lycopene and other types of carotenoids ([Giovannucci et al., 1995](#); [Khachik et al., 2002](#); [Khachik et al., 1992](#)). These carotenoids are the major source of hydrocarbons that prevent and cure malignant diseases like prostate cancer, breast cancer ([Canene-Adams et al., 2005](#)), lung cancer ([Feskanich et al., 2000](#)) and other diseases like cataracts, heart diseases ([Agarwal & Rao, 2000](#); [Rao & Rao, 2004](#); [Siemensma, 1996](#)), diabetics, hyperglycemia ([Subhash et al., 2007](#)), inflammation, arthritis ([Ames et al., 1993](#)), immune system decline, brain dysfunction ([Halliwell, 1996](#); [Petr & Erdman, 2005](#)) and maintenance of body homeostasis ([O'Kennedy et al., 2006](#)).

Flavonoids are another diverse group of chemicals in tomatoes, with an estimated daily intake of 0.023 to 1 gm/day in the human diet. Flavonoids are plant polyphenolic compounds and vary due to the C ring structure, predominantly including flavanones, flavonols, flavones, and isoflavones, flavanol ([Aruoma, 2003](#); [Vaya et al., 2003](#)). Most flavonoids are found as glycosides. Glycosides are distinguished by the presence of one or more sugar groups that are glycosidically linked to phenolic groups ([Murota & Terao, 2003](#)). Clinical trials and



epidemiological studies proved that the consumption of flavonoids plays a potential role in the management and prevention of cardiovascular and cancer diseases ([Liang et al., 2001](#)). Numerous members of this family are associated with anti-carcinogenic, anti-inflammatory, cytostatic, apoptotic, antioxidant, anti-aging, and estrogenic activities ([Breinholt & Larsen, 1998](#); [Elliott & Chithan, 2017](#); [Fotsis et al., 1997](#); [König et al., 1997](#)).

**Table 1.** Antioxidant component of tomatoes

Component	Structure Formula	Members
Lycopene		
B-Carotene		ζ-carotene, γ-carotene, neurosporene
Flavanol		(+)- catechin (-)-epicatechin Epigallocatechin gallate
Flavonol		Quercetin Kaempferol
L- Ascorbic Acid		

Quercetin is another flavonol containing a sugar group at the 3 positions, commonly distributed in a variety of plant foods ([Murota & Terao, 2003](#)). Quercetin has been shown in numerous in vitro investigations to have a wide array of biological effects, the most important of which were apoptosis induction, mutagenesis prevention, lipoxygenase inhibition, anti-allergic and superoxide dismutase-like activities, cell cycle modulation, and angiogenesis inhibition ([Formica & Regelson, 1995](#)).

Tocopherol is also regarded as a functional component, found in tomatoes ([Chang et al., 2006](#)). The tocopherols (alpha, beta, gamma, and delta tocopherols) are essential in nutrition because they have vitamin E activity. Although their in-vivo mechanism of action is still poorly known, they have also long been thought of as strong physiological antioxidants ([Azzi, 2007](#); [Traber & Atkinson, 2007](#)).

**Table 2.** Lycopene, Beta carotene, and Antioxidant content in tomatoes

Tomato varieties	Lycopene	Beta-carotene	Antioxidant Activity (%)	Total Phenolic	Reference
Cherry (Lycopersicum cerasiforme)	122 microgram/100g m	73 microgram/100g m		67 mg/100 g	<a href="#">(George et al., 2004; Guil-Guerrero &amp; Reboloso-Fuentes, 2009)</a>

Tomato ( <i>Lycopersicon esculentum</i> Mill.)	9.25 (mg/100gm )	2.34 (mg/100gm )	38 mg/100ml SEARCH	( <a href="#">Khachik et al., 2002</a> ; <a href="#">Leong &amp; Shui, 2002</a> )
Hydroponically greenhouse cluster tomatoes ( <i>Lycopersicon Escuesculentl</i> , cv. Clermon)	4.2 mg/100 g		14.92 mmol TEAC/kg.	( <a href="#">Javanmardi &amp; Kubota, 2006</a> )

---

### 3. Nutraceutical Component and Biological Effect on Human Health

The nutraceutical activity of bioactive compounds to combat diseases is understood; the activity against microbes is of greater concern in recent research activities. Increasing interest in personal health has made consumers demand safe and healthy food ([Paredes-López et al., 2010](#)). Studies in both in vitro and clinical settings have concentrated on the microbiological properties of tomatoes that can prevent *Helicobacter pylori* chronic infection. Cancer risk is also increased by oxidative load due to chronic infection ([Giovannucci, 1999](#)). *Helicobacter pylori* is also responsible for elevated DNA oxidation ([Baik et al., 1996](#)). It has been demonstrated that an extract from the fruit can block the sialic acid-specific attachment of the *H. pylori* bacteria to the human stomach mucosa. This is an essential phase in the progression of gastric ulcers ([Shmueli et al., 2004](#)).

The tomato fruit includes a variety of bioactive substances, including numerous carotenoids and antioxidant vitamins C and E ([Khachik et al., 1992](#)). Among common carotenoids, it is believed that the two antioxidants lycopene and beta-carotene are the most powerful at destroying singlet oxygen and free radicals ([Conn et al., 1991](#); [Woodall et al., 1997](#)). Oxidative damage may occur because of the imbalance caused by oxidative stress between ROS production and antioxidant defense. The pathology of many degenerative disorders, including diabetes mellitus, cancer, degenerative arthritis, CVD, macular degeneration, Alzheimer's disease, Parkinson's, multiple sclerosis, and Down syndrome, includes the production of excessive ROS, intense antioxidant defense mechanisms, and excessive ROS system activation ([Ames & Gold, 1991](#); [Liu, 2004](#); [Seeram, 2008](#); [Winterbourn, 2008](#)). Human bodies have developed a mechanism to confront stress. The process comprises exogenous antioxidants from the diet as well as endogenous antioxidants created by the body, such as non-enzymatic and enzymatic antioxidants. Antioxidant and phenolic chemicals show a variety of biologically significant mechanisms to detoxify or scavenge ROS, prevent the generation of ROS, affect the cell cycle, decrease tumor growth, alter signal transmission, control apoptosis, and regulate metabolism ([Han et al., 2007](#); [Liu, 2004](#)).

If oxidation is found to be an important factor in the development of cancer, the role of nutrition in anti-oxidation will be extremely complicated. In most cases, the effectiveness of various antioxidants is assessed using more complex experimental systems ([Bisby & Parker, 1995](#)). By reducing  $\alpha$ -tocopherol radicals, for instance, the synergistic impact of -tocopherol and ascorbic acid recycles -tocopherol. Such interactions may generate complex synergies that aid antioxidants in scavenging the various reactive oxygen species, hence enhancing the protection they provide overall ([Mortensen & Skibsted, 1997](#)). Tomatoes may be helpful to human health due to the intricate interactions that take place between the many different carotenoids, ascorbic acid, and polyphenols. These interactions may be the cause of the tomato's positive benefits.

Although it has been suggested that carotenoid compounds, particularly lycopene, may function by preventing reactive oxygen species from harming cellular macromolecules. Additionally, in vitro research shows that carotenoids inhibit the growth of a variety of cancer cells derived from insulin-like growth factor I. (IGF-I) ([Levy et al., 1995](#)). Recent research reveals that there is a favorable correlation between the elevated risk of various malignancies and the level of IGF-I in the blood. A recent study indicated that supplementing tomato products led to a significantly lower endogenous amount of strand breaks in lymphocyte DNA. Other mechanisms are also hypothesized, but most mechanistic findings have come from in vitro investigations ([Giovannucci, 1999](#); [Pool-Zobel et al., 1997](#)).



The ability of bioactive tomato components to decrease and trap free radicals has been studied using in vitro assays; typically, the antioxidant activity of a compound is determined by comparison with a standard reference. Because of the complex interactions that take place among the many distinct carotenoids, ascorbic acid, and other antioxidant polyphenolic compounds found in tomatoes, it is possible that eating tomatoes can be beneficial to human health. These interactions may be what is responsible for the favorable effects that the tomato provides ([Chang et al., 2006](#); [Huang et al., 2005](#)).

Type 2 diabetes has been demonstrated to benefit from strawberry fruit. It has been demonstrated that using strawberry fruit in various preparations, including those that are consumed whole, cooled, extracted, and even powdered, can help prevent type 2 diabetes and improve insulin sensitivity, blood vessel inflammation, endothelial dysfunction, and blood sugar regulation. Because strawberries have a low glycemic index, diabetics are less likely to experience sudden rises in blood sugar after eating them. Fibers found in strawberries help to regulate blood sugar levels as well ([Mortensen & Skibsted, 1997](#)).

**Table 3.** Trolox Equivalent Antioxidant Activities of Polyphenols in Tomatoes

Compound	TEAC (mM)	References
Quercetin	4.7 ± 0.1	( <a href="#">Rice-Evans et al., 1996</a> )
Kaempferol	1.34 ± 0.08	( <a href="#">Rice-Evans et al., 1996</a> )
Epicatechin gallate	4.9 ± 0.02	( <a href="#">Rice-Evans et al., 1996</a> )
Epigallocatechin gallate	4.8 ± 0.06	( <a href="#">Rice-Evans et al., 1996</a> )
Epigallocatechin	3.8 ± 0.06	( <a href="#">Rice-Evans et al., 1996</a> )

Attention has been drawn to how nutrition can cause disease because of the prevalence of atherosclerosis and coronary artery disease, and the need to slow their progression ([Gartside & Glueck, 1995](#); [Hu et al., 2000](#); [Joshiyura et al., 2001](#); [Kerver et al., 2003](#)). The cardiovascular system is thought to be impacted by several substances found in tomatoes, most notably carotenoid compounds, primarily lycopene ([Weisburger, 1998](#); [Willcox et al., 2003](#)). In reaction to ADP, collagen, and thrombin, the powerful antiplatelet components in tomatoes limit platelet aggregation ([Dutta-Roy, 2002](#)). Platelets are essential for cardiovascular disease development as well as hemostasis. The evidence presented suggests that the acute clinical symptoms of coronary atherosclerosis are caused by plaque breakdown and the subsequent development of platelet thrombi ([Zaman et al., 2000](#)). Both the stability of atherosclerotic plaques and disease progression may be impacted by platelet activity. We speculate that the tomato's reported cardiovascular advantages may be related to antiplatelet action and, consequently, to the inhibition of platelet function. The primary prevention of cardiovascular disease may benefit from the use of this kind of natural antithrombotic drug ([O'Kennedy et al., 2006](#)).

#### 4. Bioavailability Of Antioxidant Component in Tomato

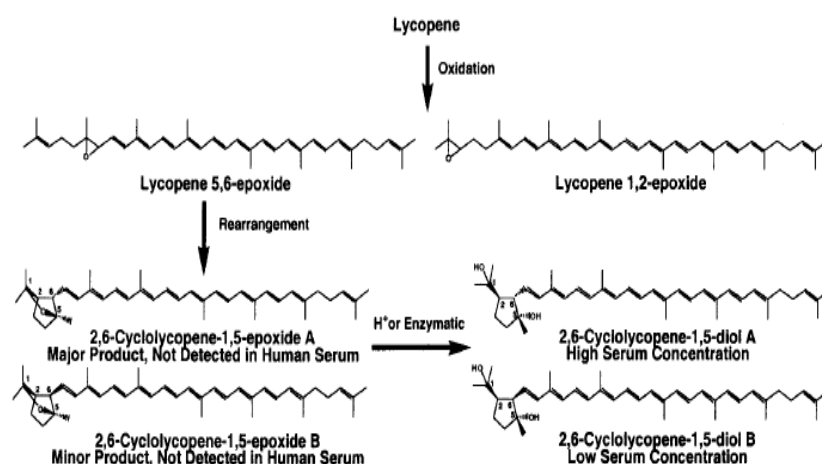
Figure 2 shows the hypothetical metabolic oxidation of lycopene in people. The research on the chemical oxidation of lycopene with m-chlorobenzene conclusively establishes that this compound undergoes first oxidation at the 1, 2, and 5, 6-positions to produce, respectively, lycopene 1, 2-epoxide and lycopene 5, 6-epoxide. However, lycopene 5, 6-epoxide was extremely unstable, and it underwent cyclization to create a mixture of 2, 6-cyclopropene-1, 5-epoxide A and B. This was the result of the cyclization process. On the other hand, lycopene 5, 6-epoxide was shown to be quite unstable, even though lycopene 1, 2-epoxide was found to be quite stable. In human serum, lycopene epoxides and lycopene 5, 6-epoxide have not been identified; nevertheless, 2, 6-cyclopropene 1,5-diols A and B, which are their corresponding cyclic diols, are primarily observed. Lycopene epoxides have also not been found ([Khachik et al., 1997](#); [Khachik et al., 1998](#)). These diols are created by the enzymatic or acidic ring opening of the corresponding epoxides. The oxidation of lycopene in human serum leads to the formation of a new five-membered ring end-group that has three asymmetric centers located at carbon atoms C-2, C-5, and C-6 ([Khachik et al., 1998](#)). There is a possibility that the traces of

these chemicals found in tomatoes and products based on tomatoes are responsible for the existence of lycopene metabolites in human serum. Because of the low quantity of these compounds in raw tomatoes and products based on tomatoes, whether or not 2,6-cyclopropene-1,5-diols A and B are present in human serum is a mystery that has not been solved ([Khachik et al., 1997](#)).

**Table 4.** Plasma lycopene of tomato products

Product	Lycopene (mg/100gm)	Serving (ml)	Lycopene (mg/100 gm)	Reference
Tomato juice	9.5	250	25	<a href="#">(Agarwal &amp; Rao, 1998)</a>
Tomato ketchup	15.9	15	2.7	<a href="#">(Hwang &amp; Bowen, 2005)</a>
Tomato paste	42.2	30	13.8	<a href="#">(Hwang &amp; Bowen, 2005)</a>
Tomato sauce	14.1	60	8.9	<a href="#">(Hwang &amp; Bowen, 2005)</a>

Lycopene oxidation may result from the natural metabolism of tomatoes, or it may happen as a result of processing tomato-based food products under harsh circumstances, such as extreme heat. These lycopene epoxides can also be produced when lycopene is oxidized in living organisms, a process known as "in vivo" or "in people." In tomatoes with a high acidity level, lycopene 5,6-epoxide has the potential to rearrange into 2,6-cyclolycopene-1,5-epoxides A and B. In the presence of acids in the human stomach, lycopene 5,6-epoxide may undergo a non-enzymatic conversion to produce 2,6-cyclolycopene-1,5-epoxides A and B, which is then followed by hydrolysis to produce each compound's respective diol. This is the outcome of the reaction. The presence of numerous lycopene metabolites in tomatoes and human serum at low concentrations may be due to lycopene's physiological activity as a radical scavenger. One wouldn't anticipate finding the resultant epoxides in the serum if lycopene is truly being oxidized in vivo in humans ([Feskanich et al., 2000](#); [Khachik et al., 1997](#)). Consequently, it is more likely that the enzymatic ring opening of the 2,6-cyclolycopene-1,5-epoxides A and B to the observed diols is involved in the metabolic oxidation of lycopene in humans. This type of enzyme may also be responsible for the conversion of lycopene epoxides into 2,6-cyclolycopene-1,5-epoxides A and B, as well as the diols A and B that correspond to these epoxides. This process occurs when lycopene epoxides are rearranged into a different structure. If lycopene 5,6-epoxide is the first product of lycopene oxidation in vivo in humans, then the enzymatic conversion of this epoxide to the cyclic diols A and B must be determined first. This conversion can take place with or without the participation of the cyclic epoxides A and B, depending on the circumstances. This transformation can take place either with or without the participation of the cyclic epoxides A and B ([Paetau et al., 1998](#)).



**Figure 2.** Lycopene metabolism ([Khachik et al., 2002](#))



According to the findings of much epidemiological research, eating tomatoes and products made from tomatoes is connected with a lower risk of developing a variety of cancers ([Giovannucci, 1999](#)). Another study examined the relationship between the consumption of various vegetables regularly and cancer deaths in 1271 senior citizens in Massachusetts. According to the study, eating a lot of tomatoes was associated with a 50% decrease in cancer-related deaths across the board. While other vegetables high in carotenoids showed little impact on disease prevention ([Rao & Agarwal, 2000](#)).

Recent research has analyzed the results of 72 epidemiological studies on tomatoes, tomato-based products, lycopene, and cancer. These investigations included ecological, case-control, dietary, and blood sample-based research ([Conn et al., 1991](#)). Numerous studies showed a negative correlation between plasma lycopene levels or tomato consumption and cancer. There are the strongest associations between different types of cancers, especially prostate, lung, and stomach. On the other hand, there was evidence of connections between cancers of the pancreas, colon and rectum, esophagus, oral mucosa, breast, and cervix. These findings were held when numerous different study designs and a variety of populations were used. None of the examined studies found evidence of higher cancer risk.

In Italy, case-control research found that eating tomatoes was consistently associated with a lower risk of cancers of the digestive system, particularly stomach, colon, and rectal cancers. The research was carried out by the National Institute of Health. In this study, cases are cancers that have been proven in the patient ([Franceschi et al., 1994](#)). Similarly, many epidemiological investigations proved an inverse association between lycopene (estimated intakes or serum levels) and breast cancer risk. However, these observations were not confirmed by other investigators ([Järvinen et al., 1997](#); [Zhang et al., 1997](#)). In a different case-control study, researchers observed that the amount of lycopene found in the serum, as well as the amount of lycopene taken in the food had an inverse association with the risk of developing cervical intraepithelial neoplasia. This was the conclusion of the researchers ([Van Eenwyk et al., 1991](#)). In yet another cohort trial, researchers showed that the levels of lycopene in serum had an inverse relationship with the chance of developing bladder cancer ([Rao & Agarwal, 2000](#)). Lycopene status appears to be inversely related to cancer risk, which can be increased by consuming foods high in this carotenoid as well as taking supplements.

Another study conducted in Hawaii found a significantly lower incidence of lung cancer; nevertheless, the same study, combining case and control groups, found only a little negative correlation between lycopene consumption and the risk of developing lung cancer that did not meet the statistical criteria for significance ([Le Marchand et al., 1993](#); [Le Marchand et al., 1989](#)). Only 29% of the lycopene intake in this population was reported to come from tomatoes. The inconsistent findings regarding tomato consumption and lycopene levels suggest that either lycopene derived from foods other than tomatoes is difficult to get or the health benefits of tomato consumption are attributed to compounds other than lycopene.

One study that discussed mesothelioma (peritoneal or pleural cancer) was available ([Muscat & Huncharek, 1996](#)). People who consume tomatoes or tomato juice 16 times or more per month have a risk that is reduced by forty percent when compared to people who do not consume either food item. Only 1.7 percent of the control participants and 9% of the case subjects said they didn't consume tomatoes or tomato juice, indicating that tomato product non-consumers have a relatively significant chance of developing mesothelioma.

The case study from China and Italy reported ([Franceschi et al., 1994](#); [Franceschi et al., 1997](#); [Hu et al., 2000](#)) about a 60% reduction in the risk of both colon and rectal cancers associated with higher tomato consumption. Lycopene and lutein, but not  $\beta$ -carotene, in a mouse model of N-methyl nitrosourea-induced colonic aberrant crypt foci, medication exhibited efficacy against this premalignant lesion in dosages that were regarded to be quite low. This activity was shown in a mouse model ([Narisawa et al., 1996](#)).

Few studies on tomatoes and lycopene with esophageal cancer have been conducted (Table 5). In Iran, where men are more likely than women to suffer esophageal cancer, according to one study, males who consume tomatoes regularly had a much lower risk of developing prostate cancer by 39%. Nevertheless, the researchers found no association between the consumption of tomatoes and the risk of developing prostate cancer in women ([Cook-Mozaffari et al., 1979](#)). In the United States, the only study that is a diet study ([Brown et al.,](#)

1988) regarding this cancer, researchers discovered a 30% reduction in the risk of esophageal cancer associated with heavy consumption of tomatoes in men. However, this reduction was not statistically significant. A serum bank study found that case patients with oral, laryngeal, or esophageal cancer had a 5% lower mean pre-diagnostic serum lycopene level than control subjects; however, based on only 28 case patients with esophageal cancer, case patients had a 16.4% lower lycopene level. This finding was not statistically significant (Giovannucci et al., 1995).

The findings of the US Health Profession Follow-up Study revealed that lycopene from various tomato products was inversely related to the risk of prostate cancer. It has been found that eating at least 10 servings of tomato products each week lowers the risk of cancer by 35%, with the preventive effects being much more pronounced for more severe or aggressive prostate cancer (Giovannucci et al., 1995). Additionally, recent case-control and cohort studies, including research on carotenoids, particularly beta-carotene, found an inverse relationship between serum and tissue levels of lycopene and the risk of developing prostate cancer (Gann et al., 1998; Nomura et al., 1997). There were four different cohort studies, and each of them came to its conclusions about the association between eating tomatoes or lycopene and an increased chance of developing prostate cancer. Consumption of tomatoes and beans, lentils, and peas was the only thing that was statistically significantly associated with a decreased risk of prostate cancer in a population of 14,000 Seventh-day Adventist men. Tomatoes have also been linked to a lower risk of bladder cancer. There was no link found between eating foods high in beta-carotene and risk (Cerhan et al., 1998; Giovannucci et al., 1995; Mills et al., 1989). In a more comprehensive investigation, researchers found no correlation between the consumption of the carotenoids  $\beta$ -carotene,  $\alpha$ -carotene, lutein, and b-cryptoxanthin with an increased risk of prostate cancer. a more in-depth investigation of the diet, but there was a correlation between a high intake of lycopene and a decrease in risk that was statistically significant by 21%. The ingestion of tomatoes and products derived from tomatoes, which accounted for 82% of the lycopene, was associated with a 35% and 53% reduction, respectively, in the risk of developing aggressive prostate cancer (Giovannucci et al., 1995). The highest inverse link between prostate cancer risk and tomato sauce was found; tomatoes and pizza were shown to have weaker inverse associations, but there was no evidence of such a relationship with tomato juice. Initial findings from two separate studies using cohorts (Cerhan et al., 1998; Giovannucci et al., 1995; Mills et al., 1989) Also support this finding.

Three studies looked at lycopene levels in serum in connection with cervical cancer (Batieha et al., 1993; Potischman et al., 1991), or precursor lesions (Van Eenwyk et al., 1991), while two studies looked at tomato consumption and the risk of cervical cancer (de Vet et al., 1991; Marshall et al., 1983). In one case-control investigation (Marshall et al., 1983). There were three studies conducted that investigated the relationship between lycopene levels in serum and cervical cancer. According to a study by de Vet et al. (1991), women who consumed tomatoes at least thrice per week had a 40% lower risk of developing cervical dysplasia compared to women who did not consume tomatoes.

There was only one study that published any information on tomatoes or lycopene concerning ovarian cancer, so this is all we have to go on. 35 case subjects participated in this prospective serum-based investigation (Helzlsouer et al., 1996). Even though the case participants' mean serum lycopene levels were 7.4 lower than those of the control, this tiny investigation found no correlation. Before more definitive judgments can be drawn about this cancer, more research is necessary.

**Table 5.** Pharmacokinetic parameters in human

Type of Cancer	Type of Study	No. of case study	Exposure	%age reduction in risk	Reference
Lungs and Pleura	Case-control	230♂ 102♀	Quintile 5 vs. 1 Lycopene consumption from tomatoes Quintile 5 vs. Quintile 1	29%	(Le Marchand et al., 1993)



Lungs and Pleura	Case-control (mesothelioma)	94	Tomato/tomato juice consumption, 0/mo	40%	( <a href="#">Muscat &amp; Huncharek, 1996</a> )
Colorectal	Case-control (colon, rectal)	111 C 225 R	1966 diet (>15 kg/y) 1985 diet (>15 kg/y) ♂ rectal 1966 >20 kg/y	60%	( <a href="#">Hu et al., 2000</a> )
Colorectal	Case-control (colon, rectal)	955 C 629 R	Quartile 4 vs. 1 Tomato	60%	( <a href="#">Franceschi et al., 1997</a> )
Esophageal and laryngeal	Case-control (esophagus)	217 ♂ 127 ♀	Raw tomato intake, ≥1/wk vs. <1/mo	39%	( <a href="#">Cook-Mozaffari et al., 1979</a> )
Esophageal and laryngeal	Case-control (esophagus)	207 ♂	Tomatoes, high vs. low intake	30%	( <a href="#">Giovannucci et al., 1995</a> )
Prostate	Cohort	773	>10 servings of tomato-based goods per week compared. 1.5 servings per week Tomato sauce consumption, 2-4 vs. 0/wk	21%	( <a href="#">Giovannucci et al., 1995</a> )
Prostate	Cohort	328	Intake of lycopene in the diet, 718 mg vs. 402 mg 5 raw tomatoes per week vs. 3 per month Cooked tomato consumption, 2/wk vs. 1/mo	35%	( <a href="#">Kays, 1991</a> )
Cervical cancer	Case-control (Cervical dysplasia)	257	Tomato intake, ≥3 vs. 0/wk	40%	( <a href="#">de Vet et al., 1991</a> )
Ovarian	Cohort	35	Serum lycopene level, >35.2 mg/dL vs. <21.9 mg/dL	7.4%	( <a href="#">Helzlsouer et al., 1996</a> )

Ingestion of tomato juice prevented male Fischer 344 rats from developing urinary bladder transitional cell carcinomas that were generated by N-butyl-N-(4-hydroxy butyl) nitrosamine ([Okajima et al., 1998](#)). Recent research has shown that ingesting lycopene at a concentration of 10 parts per million (ppm) significantly reduces the oxidation of lipids and proteins and appears to protect against colonic preneoplastic lesions brought

on by azoxymethane. In the rat colon model, it was also shown that dietary lycopene in the form of vegetable juice was protective against AOM-induced aberrant crypt foci ([Arimochi et al., 1999](#)).

Male mouse lung adenomas and carcinomas caused by diethylnitrosamine, methyl nitrosourea, and dimethylhydrazine were considerably reduced by dietary lycopene dissolved in water at a level of 50 ppm ([Kim et al., 1997](#)). However, female mice did not exhibit the lung cancer prevention benefits of lycopene. In the same study, dietary lycopene had no impact on kidney or colon cancers. The tobacco-smoke carcinogens benzo[a]pyrene and 4-[methyl]nitrosamino were not affected by dietary lycopene therapy in another investigation. 1. [3-pyridyl] lung tumor multiplication brought on by 1-butanone in A/J mice (Hecht et al. 1999). The absence of DNA oxidation in this animal was presumably the cause of the lack of protection against benzopyrene-induced lung cancers.

In the study, 12-week-old Wistar rats treated with intraperitoneal ferric nitrilotriacetate (Fe-NTA) (10 mg Fe/kg) had their plasma and prostate carotenoid concentrations assessed for oxidative DNA damage. Plasma concentrations of beta-carotene and lycopene were measured as a function of time in rats that had been given carotenoids intraperitoneally (10 mg kg<sup>-1</sup> day<sup>-1</sup> of either lycopene or beta-carotene). After receiving an intravenous injection of lycopene or beta-carotene, the peak total plasma concentration was reached three or six hours later, depending on which compound was administered. After five days of treatment with carotenoid therapy, the levels of lycopene and beta-carotene in the prostate were in the range of 0.10-0.51 nmol/g of wet tissue. The amount of 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodGuo) in rat prostate DNA was considerably higher 3 hours after Fe-NTA injection (6.3 0.6 residues/106 dGuo) compared to control rats (1.7 0.3 residues/106 dGuo) using a sensitive method to detect 8-oxodGuo by HPLC/EC. Before receiving Fe-NTA treatment, rats given lycopene or β-carotene showed a 70% drop in 8-oxodGuo levels, bringing them close to control levels. The buildup of malondialdehyde in the prostate of Fe-NTA-treated rats was 78% higher than that of control rats. Pre-treatment with lycopene or βcarotene virtually eliminated lipid degradation ([Rao & Agarwal, 2000](#)).

Atherosclerosis, the condition that underlies heart attacks and ischemic strokes, is thought to be caused in part by the oxidation of LDL, which transports cholesterol into the bloodstream ([Parthasarathy et al., 1992](#); [Witztum, 1994](#)). Because they can prevent harmful oxidative processes, antioxidant foods are thought to reduce the development of atherosclerosis ([Hodis et al., 1995](#); [Parthasarathy et al., 1992](#)). Various epidemiological studies have demonstrated vitamin E's beneficial effects, which are attributed to its antioxidant characteristics ([Morris et al., 1994](#); [Timlin & Pereira, 2007](#)). However, multiple studies on dietary interventions using α-tocopherol or β-carotene have shown conflicting findings. Lycopene-related studies have not been carried out.

In several epidemiological studies, a decreased risk of getting CVD has been associated with increased plasma lycopene levels ([Petr & Erdman, 2005](#)). For instance, in the Kuopio Ischemic Heart Disease Risk Factor Study, researchers investigated the relationship between serum antioxidant levels and the intima-mediated thickness of the common carotid artery (CCA-IMT). The CCA-IMT is a measurement that is associated with the probability of having an acute coronary episode. They found that those who had a cardiac event had lower levels of plasma lycopene than those who did not have a cardiac incident ([Rissanen et al., 2002](#); [Rissanen et al., 2003](#)). Additionally, a lower mean and maximal CCA-IMT with low lycopene was inversely linked with a greater serum lycopene concentration, leading to an 18% rise in CCA-IMT.

Since 1984, cardiovascular diseases have been the cause of death for one person every minute, resulting in the deaths of half a million women annually, more women than men.<sup>27</sup> The Women's Health Study is a trial that is currently being conducted and is randomized, double-blind, placebo-controlled, and two-factorial. The purpose of the study is to investigate how aspirin and vitamin E increase the likelihood of cancer and cardiovascular disease developing in women. Women who consumed 1.5 to 4 servings a week, 4 to 7 servings per week, 7 to 10 servings a week, or 10 servings a week were compared to ladies who consumed the fewest tomatoes overall in the first quintile. The participants were provided with FFQs to fill out. The relative risks of cardiovascular disease (CVD) associated with eating tomatoes were 1.02, 1.04, 0.68, and 0.71, respectively. In addition to this, it was shown that consuming a greater quantity of tomatoes, as opposed to lycopene, was more significantly associated with a reduced risk of developing cardiovascular disease ([Sesso et al., 2003](#)).



Antiplatelet aggregation is also linked to tomato consumption. Components of tomato extract seem to inhibit glycoprotein IIb/IIIa and platelet secretory processes, which in turn appear to be connected to the suppression of ADP-, collagen-, thrombin-, and arachidonate-mediated platelet aggregation. After supplementing for 3 hours with a dose of tomato extract equal to 6 tomatoes, they discovered a significant reduction of baseline platelet function, decreasing it from 2.9 1.4% to 20.0 4.9% ([O'Kennedy et al., 2006](#)).

**Table 6.** Pharmacokinetic Parameters in Human Cardiovascular Diseases

Type of Study	Target specie	Dose	Response (Relative risk)	Reference
Double-blind, placebo-controlled 2 _ 2 factorial	Women	1.5 to <4, 4 to <7, 7 to <10, or ≥10 a week	1.02, 1.04, 0.68, and 0.71	( <a href="#">Canene-Adams et al., 2005</a> )
In vitro platelet aggregation	Male and Female. 16 to 60 years of age	18 gm extract syrup	2.9 ± 1.4% to 20.0±4.9% inhibition baseline platelet function	( <a href="#">O'Kennedy et al., 2006</a> )

To increase the variety of exposure within the trial, participants in the recent multicenter case-control study (EURAMIC) were drawn from ten different European nations. Only lycopene levels, not  $\beta$ -carotene levels, were found to be protective when several dietary factors were taken into account ([Huttunen, 1997](#)). Lycopene's preventive potential was greatest in those with the highest polyunsaturated fat reserves, lending credence to the antioxidant notion. In a concurrent cross-sectional investigation, it was discovered that decreased blood lycopene levels were likewise linked to an increased risk of mortality from CVD ([Kristenson et al., 1997](#)). The epidemiological studies conducted to date have a variety of limitations, including, but not limited to, the heterogeneous population, blood carotenoid levels, duration of the investigation, and illness biomarkers. More research should be undertaken with these study criteria in mind to provide a more definite function for lycopene in disease prevention.

## 5. Toxicity

A few intervention trials show, in contrast to much observational research, that dietary supplementation with high quantities of carotenoids, including lycopene, has no utility in preventing human disease and may even increase disease incidence for risk groups. An eating problem called lycopenaemia is brought on by consuming too many tomatoes, which are high in lycopene ([Reich et al., 1960](#)). The pigment is secreted by the sudoral and sebaceous glands after consumption and is partially reabsorbed by the keratin layer of the skin ([Bonnetblanc et al., 1987](#)). On the forehead, nasolabial folds, palms, and soles, a "yellow-orange" pigmentation was seen. The patient has been experiencing stomach aches for a few months. In actuality, the pigment tends to accumulate in specific regions of the liver and congeals into "fatty cysts," causing microscopic and macroscopic changes to the parenchyma.

Lycopene has been used in rat feeding trials lasting four to fourteen weeks, as well as embryotoxicity/teratogenicity research that has all been published as standard repeated dosage animal toxicity data ([Jonker et al., 2003](#)). The lycopene bead formulation was well tolerated by rats in the 4-week study at a dose of 1000 mg/kg body weight/day. At doses of up to 500 mg lycopene/kg body weight/day, rats were treated with a beadle formulation for 14 weeks with no adverse effects. A dose-related orange-red staining of the liver and adipose tissue was seen, particularly in females, and it only partially dissipated after a five-week recovery period. This was detected in both the liver and the adipose tissue. At the high and mid-doses (150 mg/kg body weight/day), there were small alterations in hematological parameters, and, in one sex only, there were changes in the thyroid and brain's relative weights. In this investigation, no morphological or histological changes caused by the therapy were noted. At a dose of 1000mg lycopene/kg body weight/day, the pups'

embryotoxicity study found an increase in the number of complete extra thoracic ribs (14th rib). In a recent 13-week oral toxicity trial that complied with GLP standards, rats were given two more synthetic lycopene products by daily oral gavage in water. The products contained a stabilizing formulation matrix that contained around 10% synthetic lycopene ([Mellert et al., 2002](#)). The maximum dose level assessed in the above investigation, approximately 300 mg of lycopene per kilogram of body weight per day, was a NOAEL.

Intake of flavonoids, particularly quercetin, and cancer, particularly lung cancer, were found to be negatively correlated in the [Kroon and Williamson \(2005\)](#) study, which involved approximately 10,000 participants. It appears that bio-phenols are hazardous to cancer cells that are growing quickly, but not to healthy cells. Actually, despite the results of a sizeable majority of studies indicating that bio-phenols have no effect, no dietary intervention studies have yet demonstrated a negative effect that bio-phenols have. According to the findings of a toxicological study, the administration of a mega dose of grape seed proanthocyanidin extract equaling 2 grams per kilogram of body weight did not result in any discernible toxicity ([Knekt et al., 1997](#)).

## 6. Conclusion

There has been a growth in research expertise, understanding, and application of practical methodology pertinent to bioactive substances in recent years. This expansion can be ascribed to a variety of sources. The discovery of alternative medicines that utilize tomato compounds for the prevention and management of illnesses caused by antibiotic-resistant bacteria will also be a major future concern in establishing research priorities in the coming years. Tomato compounds with antioxidant characteristics have many potential applications in the food industry and medicine as natural antibacterial agents. In our opinion, the synthesis of chemicals for the sake of nutrition and health should be given a higher priority and more attention. Techniques like plant breeding and genetic analysis come into play here.

### CRediT authorship contribution statement

Muhammad Suhail Ibrahim, Ahmed Mujtaba, and Ishtiaq Hassan, Experiment and analyze data, Wajahat Azeem, Muhammad Waqar, Itrat Fatima, Muhammad Nadeem, Data analysis, writing-original draft, Asma Sohail, Kashif Sarfraz Abbasi, and Abdus Samee, editing, proofreading.

### Funding

This work was not financially supported by any funding agency.

### Declaration of Competing Interest

The authors declare no conflict of interest.

### Acknowledgments

The author(s) acknowledge that they did not receive any financial support from any funding agency, whether public, private, or non-profit. The study was conducted independently without external funding.

### References

- Abushita, A. A., Hebshi, E. A., Daood, H. G., & Biacs, P. A. (1997). Determination of antioxidant vitamins in tomatoes. *Food chemistry*, 60(2), 207-212.
- Agarwal, S., & Rao, A. V. (1998). Tomato lycopene and low density lipoprotein oxidation: a human dietary intervention study. *Lipids*, 33(10), 981-984.
- Agarwal, S., & Rao, A. V. (2000). Tomato lycopene and its role in human health and chronic diseases. *Cmaj*, 163(6), 739-744.
- Ames, B. N., & Gold, L. S. (1991). Endogenous mutagens and the causes of aging and cancer. *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis*, 250(1-2), 3-16.
- Ames, B. N., Shigenaga, M. K., & Hagen, T. M. (1993). Oxidants, antioxidants, and the degenerative diseases of aging. *Proceedings of the National Academy of Sciences*, 90(17), 7915-7922.
- Arimochi, H., Kataoka, K., Kuwahara, T., Nakayama, H., Misawa, N., & Ohnishi, Y. (1999). Effects of  $\beta$ -glucuronidase-deficient and lycopene-producing *Escherichia coli* strains on formation of azoxymethane-induced aberrant crypt foci in the rat colon. *Biochemical and Biophysical Research Communications*, 262(2), 322-327.
- Aruoma, O. I. (2003). Methodological considerations for characterizing potential antioxidant actions of bioactive components in plant foods. *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis*, 523, 9-20.



- Azzi, A. (2007). Molecular mechanism of  $\alpha$ -tocopherol action. *Free Radical Biology and Medicine*, 43(1), 16-21.
- Baik, S.-C., Youn, H.-S., Chung, M.-H., Lee, W.-K., Cho, M.-J., Ko, G.-H., Park, C.-K., Kasai, H., & Rhee, K.-H. (1996). Increased oxidative DNA damage in *Helicobacter pylori*-infected human gastric mucosa. *Cancer research*, 56(6), 1279-1282.
- Batieha, A. M., Armenian, H. K., Norkus, E. P., Morris, J. S., Spate, V. E., & Comstock, G. W. (1993). Serum micronutrients and the subsequent risk of cervical cancer in a population-based nested case-control study. *Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology*, 2(4), 335-339.
- Bisby, R. H., & Parker, A. W. (1995). Reaction of ascorbate with the  $\alpha$ -tocopheroxyl radical in micellar and bilayer membrane systems. *Archives of biochemistry and biophysics*, 317(1), 170-178.
- Block, G., Patterson, B., & Subar, A. (1992). Fruit, vegetables, and cancer prevention: a review of the epidemiological evidence. *Nutrition and cancer*, 18(1), 1-29.
- Bonnetblanc, J.-M., Bonafé, J.-L., & Vidal, E. (1987). Caroténodermies diététiques. *Annales de dermatologie et de vénéréologie*,
- Breinholt, V., & Larsen, J. C. (1998). Detection of weak estrogenic flavonoids using a recombinant yeast strain and a modified MCF7 cell proliferation assay. *Chemical research in toxicology*, 11(6), 622-629.
- Brown, L. M., Blot, W. J., Schuman, S. H., Smith, V. M., Ershow, A. G., Marks, R. D., & Fraumeni Jr, J. F. (1988). Environmental factors and high risk of esophageal cancer among men in coastal South Carolina. *JNCI: Journal of the National Cancer Institute*, 80(20), 1620-1625.
- Canene-Adams, K., Campbell, J. K., Zaripheh, S., Jeffery, E. H., & Erdman Jr, J. W. (2005). The tomato as a functional food. *The Journal of Nutrition*, 135(5), 1226-1230.
- Cerhan, J., Chiu, B., Putnam, S., Parker, A., Robbins, M., Lynch, C., Cantor, K., Torner, J., & Wallace, R. (1998). A cohort study of diet and prostate cancer risk. *Cancer Epidemiol Biomarkers Prev*, 7, 175.
- Chang, C.-H., Lin, H.-Y., Chang, C.-Y., & Liu, Y.-C. (2006). Comparisons on the antioxidant properties of fresh, freeze-dried and hot-air-dried tomatoes. *Journal of Food Engineering*, 77(3), 478-485.
- Conn, P. F., Schalch, W., & Truscott, T. G. (1991). The singlet oxygen and carotenoid interaction. *Journal of Photochemistry and Photobiology B: Biology*, 11(1), 41-47.
- Cook-Mozaffari, P., Azordegan, F., Day, N., Ressaoud, A., Sabai, C., & Aramesh, B. (1979). Oesophageal cancer studies in the Caspian Littoral of Iran: results of a case-control study. *British journal of cancer*, 39(3), 293-309.
- de Vet, H. C., KNIPSCHILD, P. G., GROL, M. E., SCHOUTEN, H. J., & STURMANS, F. (1991). The role of beta-carotene and other dietary factors in the aetiology of cervical dysplasia: results of a case-control study. *International journal of epidemiology*, 20(3), 603-610.
- Dutta-Roy, A. K. (2002). Dietary components and human platelet activity. *Platelets*, 13(2), 67-75.
- Elliott, M., & Chithan, K. (2017). The impact of plant flavonoids on mammalian biology: implications for immunity, inflammation and cancer. In *The flavonoids advances in research since 1986* (pp. 619-652). Routledge.
- Feskanich, D., Ziegler, R. G., Michaud, D. S., Giovannucci, E. L., Speizer, F. E., Willett, W. C., & Colditz, G. A. (2000). Prospective study of fruit and vegetable consumption and risk of lung cancer among men and women. *Journal of the National Cancer Institute*, 92(22), 1812-1823.
- Formica, J., & Regelson, W. (1995). Review of the biology of quercetin and related bioflavonoids. *Food and chemical toxicology*, 33(12), 1061-1080.
- Fotsis, T., Pepper, M. S., Aktas, E., Breit, S., Rasku, S., Adlercreutz, H., Wähälä, K., Montesano, R., & Schweigerer, L. (1997). Flavonoids, dietary-derived inhibitors of cell proliferation and in vitro angiogenesis. *Cancer research*, 57(14), 2916-2921.
- Franceschi, S., Bidoli, E., Vecchia, C. L., Talamini, R., D'Avanzo, B., & Negri, E. (1994). Tomatoes and risk of digestive-tract cancers. *International journal of cancer*, 59(2), 181-184.
- Franceschi, S., Favero, A., La Vecchia, C., Negri, E., Conti, E., Montella, M., Giacosa, A., Nanni, O., & Decarli, A. (1997). Food groups and risk of colorectal cancer in Italy. *International journal of cancer*, 72(1), 56-61.
- Gann, P., Ma, J., Giovannucci, E., Willett, W., Sacks, F., Hennekens, C., & Stampfer, M. (1998). Prospective analysis of plasma antioxidants and prostate cancer risk. *Proc Am Assoc Cancer Res*,
- Gartside, P., & Glueck, C. (1995). The important role of modifiable dietary and behavioral characteristics in the causation and prevention of coronary heart disease hospitalization and mortality: the prospective NHANES I follow-up study. *Journal of the American College of Nutrition*, 14(1), 71-79.

- George, B., Kaur, C., Khurdiya, D., & Kapoor, H. (2004). Antioxidants in tomato (*Lycopersium esculentum*) as a function of genotype. *Food chemistry*, 84(1), 45-51.
- Giovanelli, G., Lavelli, V., Peri, C., & Nobili, S. (1999). Variation in antioxidant components of tomato during vine and post-harvest ripening. *Journal of the Science of Food and Agriculture*, 79(12), 1583-1588.
- Giovannucci, E. (1999). Tomatoes, tomato-based products, lycopene, and cancer: review of the epidemiologic literature. *Journal of the National Cancer Institute*, 91(4), 317-331.
- Giovannucci, E., Ascherio, A., Rimm, E. B., Stampfer, M. J., Colditz, G. A., & Willett, W. C. (1995). Intake of carotenoids and retino in relation to risk of prostate cancer. *JNCI Journal of the National Cancer Institute*, 87(23), 1767-1776.
- Guil-Guerrero, J., & Reboloso-Fuentes, M. (2009). Nutrient composition and antioxidant activity of eight tomato (*Lycopersicon esculentum*) varieties. *Journal of Food Composition and analysis*, 22(2), 123-129.
- Halliwell, B. (1996). Antioxidants in human health and disease. *Annual review of nutrition*, 16(1), 33-50.
- Han, X., Shen, T., & Lou, H. (2007). Dietary polyphenols and their biological significance. *International journal of molecular sciences*, 8(9), 950-988.
- Helzlsouer, K. J., Alberg, A. J., Norkus, E. P., Morris, J. S., Hoffman, S. C., & Comstock, G. W. (1996). Prospective study of serum micronutrients and ovarian cancer. *JNCI: Journal of the National Cancer Institute*, 88(1), 32-37.
- Hodis, H. N., Mack, W. J., LaBree, L., Cashin-Hemphill, L., Sevastian, A., Johnson, R., & Azen, S. P. (1995). Serial coronary angiographic evidence that antioxidant vitamin intake reduces progression of coronary artery atherosclerosis. *Jama*, 273(23), 1849-1854.
- Hu, F. B., Rimm, E. B., Stampfer, M. J., Ascherio, A., Spiegelman, D., & Willett, W. C. (2000). Prospective study of major dietary patterns and risk of coronary heart disease in men. *The American journal of clinical nutrition*, 72(4), 912-921.
- Huang, D., Ou, B., & Prior, R. L. (2005). The chemistry behind antioxidant capacity assays. *Journal of agricultural and food chemistry*, 53(6), 1841-1856.
- Huttunen, J. (1997). Lycopene and myocardial infarction risk in the EURAMIC Study. *American journal of epidemiology*.
- Hwang, E. S., & Bowen, P. E. (2005). Effects of lycopene and tomato paste extracts on DNA and lipid oxidation in LNCaP human prostate cancer cells. *Biofactors*, 23(2), 97-105.
- Järvinen, R., Knekt, P., Seppänen, R., & Teppo, L. (1997). Diet and breast cancer risk in a cohort of Finnish women. *Cancer letters*, 114(1-2), 251-253.
- Javanmardi, J., & Kubota, C. (2006). Variation of lycopene, antioxidant activity, total soluble solids and weight loss of tomato during postharvest storage. *Postharvest Biology and Technology*, 41(2), 151-155.
- Jonker, D., Kuper, C., Fraile, N., Estrella, A., & Otero, C. R. g. (2003). Ninety-day oral toxicity study of lycopene from *Blakeslea trispora* in rats. *Regulatory Toxicology and Pharmacology*, 37(3), 396-406.
- Joshiyura, K. J., Hu, F. B., Manson, J. E., Stampfer, M. J., Rimm, E. B., Speizer, F. E., Colditz, G., Ascherio, A., Rosner, B., & Spiegelman, D. (2001). The effect of fruit and vegetable intake on risk for coronary heart disease. *Annals of internal medicine*, 134(12), 1106-1114.
- Kays, S. J. (1991). *Postharvest physiology and handling of perishable plant products*.
- Kerver, J. M., Yang, E. J., Bianchi, L., & Song, W. O. (2003). Dietary patterns associated with risk factors for cardiovascular disease in healthy US adults. *The American journal of clinical nutrition*, 78(6), 1103-1110.
- Khachik, F., Carvalho, L., Bernstein, P. S., Muir, G. J., Zhao, D.-Y., & Katz, N. B. (2002). Chemistry, distribution, and metabolism of tomato carotenoids and their impact on human health. *Experimental biology and medicine*, 227(10), 845-851.
- Khachik, F., Goli, M. B., Beecher, G. R., Holden, J., Lusby, W. R., Tenorio, M. D., & Barrera, M. R. (1992). Effect of food preparation on qualitative and quantitative distribution of major carotenoid constituents of tomatoes and several green vegetables. *Journal of agricultural and food chemistry*, 40(3), 390-398.
- Khachik, F., Spangler, C. J., Smith, J. C., Canfield, L. M., Steck, A., & Pfander, H. (1997). Identification, quantification, and relative concentrations of carotenoids and their metabolites in human milk and serum. *Analytical chemistry*, 69(10), 1873-1881.
- Khachik, F., Steck, A., Niggli, U. A., & Pfander, H. (1998). Partial synthesis and structural elucidation of the oxidative metabolites of lycopene identified in tomato paste, tomato juice, and human serum. *Journal of agricultural and food chemistry*, 46(12), 4874-4884.



- Kim, D. J., Takasuka, N., Kim, J. M., Sekine, K., Ota, T., Asamoto, M., Murakoshi, M., Nishino, H., Nir, Z., & Tsuda, H. (1997). Chemoprevention by lycopene of mouse lung neoplasia after combined initiation treatment with DEN, MNU and DMH. *Cancer letters*, 120(1), 15-22.
- Knekt, P., Järvinen, R., Seppänen, R., Heliövaara, M., Teppo, L., Pukkala, E., & Aromaa, A. (1997). Dietary flavonoids and the risk of lung cancer and other malignant neoplasms. *American journal of epidemiology*, 146(3), 223-230.
- König, A., Schwartz, G. K., Mohammad, R. M., Al-Katib, A., & Gabilove, J. L. (1997). The novel cyclin-dependent kinase inhibitor flavopiridol downregulates Bcl-2 and induces growth arrest and apoptosis in chronic B-cell leukemia lines. *Blood, The Journal of the American Society of Hematology*, 90(11), 4307-4312.
- Kristenson, M., Zieden, B., Kucinskiene, Z., Abaravicius, A., Razinkovienė, L., Elinder, L. S., Bergdahl, B., Elwing, B., Calkauskas, H., & Olsson, A. G. (1997). Antioxidant state and mortality from coronary heart disease in Lithuanian and Swedish men: concomitant cross sectional study of men aged 50. *bmj*, 314(7081), 629.
- Kroon, P., & Williamson, G. (2005). Polyphenols: dietary components with established benefits to health? *Journal of the Science of Food and Agriculture*, 85(8), 1239-1240.
- Lafay, S., & Gil-Izquierdo, A. (2008). Bioavailability of phenolic acids. *Phytochemistry Reviews*, 7(2), 301-311.
- Le Marchand, L., Hankin, J. H., Kolonel, L. N., Beecher, G. R., Wilkens, L. R., & Zhao, L. P. (1993). Intake of specific carotenoids and lung cancer risk. *Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology*, 2(3), 183-187.
- Le Marchand, L., Yoshizawa, C. N., Kolonel, L. N., Hankin, J. H., & Goodman, M. T. (1989). Vegetable consumption and lung cancer risk: a population-based case-control study in Hawaii. *JNCI: Journal of the National Cancer Institute*, 81(15), 1158-1164.
- Lee, S. K., & Kader, A. A. (2000). Preharvest and postharvest factors influencing vitamin C content of horticultural crops. *Postharvest Biology and Technology*, 20(3), 207-220.
- Leong, L., & Shui, G. (2002). An investigation of antioxidant capacity of fruits in Singapore markets. *Food chemistry*, 76(1), 69-75.
- Levy, J., Bosin, E., Feldman, B., Giat, Y., Miinster, A., Danilenko, M., & Sharoni, Y. (1995). Lycopene is a more potent inhibitor of human cancer cell proliferation than either  $\alpha$ -carotene or  $\beta$ -carotene.
- Liang, Y.-C., Tsai, S.-H., Tsai, D.-C., Lin-Shiau, S.-Y., & Lin, J.-K. (2001). Suppression of inducible cyclooxygenase and nitric oxide synthase through activation of peroxisome proliferator-activated receptor- $\gamma$  by flavonoids in mouse macrophages. *FEBS letters*, 496(1), 12-18.
- Liu, R. H. (2004). Potential synergy of phytochemicals in cancer prevention: mechanism of action. *The Journal of Nutrition*, 134(12), 3479S-3485S.
- Marshall, J. R., Graham, S., Byers, T., Swanson, M., & Brasure, J. (1983). Diet and smoking in the epidemiology of cancer of the cervix. *Journal of the National Cancer Institute*, 70(5), 847-851.
- Mellert, W., Deckardt, K., Gembardt, C., Schulte, S., Van Ravenzwaay, B., & Slesinski, R. (2002). Thirteen-week oral toxicity study of synthetic lycopene products in rats. *Food and chemical toxicology*, 40(11), 1581-1588.
- Miller, N. J., Sampson, J., Candeias, L. P., Bramley, P. M., & Rice-Evans, C. A. (1996). Antioxidant activities of carotenes and xanthophylls. *FEBS letters*, 384(3), 240-242.
- Mills, P. K., Beeson, W. L., Phillips, R. L., & Fraser, G. E. (1989). Cohort study of diet, lifestyle, and prostate cancer in Adventist men. *Cancer*, 64(3), 598-604.
- Morris, D. L., Kritchevsky, S. B., & Davis, C. (1994). Serum carotenoids and coronary heart disease: the lipid research clinics coronary primary prevention trial and follow-up study. *Jama*, 272(18), 1439-1441.
- Mortensen, A., & Skibsted, L. H. (1997). Real time detection of reactions between radicals of lycopene and tocopherol homologues. *Free radical research*, 27(2), 229-234.
- Murota, K., & Terao, J. (2003). Antioxidative flavonoid quercetin: implication of its intestinal absorption and metabolism. *Archives of biochemistry and biophysics*, 417(1), 12-17.
- Muscat, J., & Huncharek, M. (1996). Dietary intake and the risk of malignant mesothelioma. *British journal of cancer*, 73(9), 1122-1125.
- Narisawa, T., Fukaura, Y., Hasebe, M., Ito, M., Aizawa, R., Murakoshi, M., Uemura, S., Khachik, F., & Nishino, H. (1996). Inhibitory effects of natural carotenoids,  $\alpha$ -carotene,  $\beta$ -carotene, lycopene and lutein, on colonic aberrant crypt foci formation in rats. *Cancer letters*, 107(1), 137-142.

- Nomura, A., Ziegler, R. G., Stemmermann, G. N., Chyou, P.-H., & Craft, N. E. (1997). Serum micronutrients and upper aerodigestive tract cancer. *Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology*, 6(6), 407-412.
- O'Kennedy, N., Crosbie, L., van Lieshout, M., Broom, J. I., Webb, D. J., & Duttaroy, A. K. (2006). Effects of antiplatelet components of tomato extract on platelet function in vitro and ex vivo: a time-course cannulation study in healthy humans. *The American journal of clinical nutrition*, 84(3), 570-579.
- Okajima, E., Tsutsumi, M., Ozono, S., Akai, H., Denda, A., Nishino, H., Oshima, S., Sakamoto, H., & Konishi, Y. (1998). Inhibitory effect of tomato juice on rat urinary bladder carcinogenesis after N-butyl-N-(4-hydroxybutyl) nitrosamine initiation. *Japanese journal of cancer research*, 89(1), 22-26.
- Organization, W. H. (2002). *The world health report 2002: reducing risks, promoting healthy life*. World Health Organization.
- Oshima, S., Ojima, F., Sakamoto, H., Ishiguro, Y., & Terao, J. (1996). Supplementation with carotenoids inhibits singlet oxygen-mediated oxidation of human plasma low-density lipoprotein. *Journal of agricultural and food chemistry*, 44(8), 2306-2309.
- Paetau, I., Khachik, F., Beecher, G. R., Kramer, T. R., Chittams, J., & Clevidence, B. A. (1998). Chronic ingestion of lycopene-rich tomato juice or lycopene supplements significantly increases plasma concentrations of lycopene and related tomato carotenoids in humans. *The American journal of clinical nutrition*, 68(6), 1187-1195.
- Paredes-López, O., Cervantes-Ceja, M. L., Vigna-Pérez, M., & Hernández-Pérez, T. (2010). Berries: improving human health and healthy aging, and promoting quality life – a review. *Plant Foods for Human Nutrition*, 65(3), 299-308.
- Parthasarathy, S., Steinberg, D., & Witztum, J. (1992). The role of oxidized low-density lipoproteins in the pathogenesis of atherosclerosis. *Annual review of medicine*, 43, 219-225.
- Petr, L., & Erdman, J. (2005). Lycopene and risk of cardiovascular disease. *Carotenoids and retinoids: Biological actions and human health*, 204-217.
- Pila, N., Gol, N. B., & Rao, T. R. (2010). Effect of post harvest treatments on physicochemical characteristics and shelf life of tomato (*Lycopersicon esculentum* Mill.) fruits during storage. *American-Eurasian Journal of Agricultural and Environmental Sciences*, 9(5), 470-479.
- Pool-Zobel, B., Bub, A., Müller, H., Wollowski, I., & Rechkemmer, G. (1997). Consumption of vegetables reduces genetic damage in humans: first results of a human intervention trial with carotenoid-rich foods. *Carcinogenesis*, 18(9), 1847-1850.
- Potischman, N., Herrero, R., Brinton, L. A., Reeves, W. C., Stacewicz-Sapuntzakis, M., Jones, C. J., Brenes, M. M., Tenorio, F., de Britton, R. C., & Gaitan, E. (1991). A case-control study of nutrient status and invasive cervical cancer: II. Serologic indicators. *American journal of epidemiology*, 134(11), 1347-1355.
- Rao, A., & Rao, L. (2004). Lycopene and human health.
- Rao, A. V., & Agarwal, S. (2000). Role of antioxidant lycopene in cancer and heart disease. *Journal of the American College of Nutrition*, 19(5), 563-569.
- Reich, P., Shwachman, H., & Craig, J. M. (1960). Lycopopenia: a variant of carotenemia. *New England Journal of Medicine*, 262(6), 263-269.
- Rice-Evans, C. A., Miller, N. J., & Paganga, G. (1996). Structure-antioxidant activity relationships of flavonoids and phenolic acids. *Free Radical Biology and Medicine*, 20(7), 933-956.
- Rissanen, T., Voutilainen, S., Nyyssönen, K., & Salonen, J. T. (2002). Lycopene, atherosclerosis, and coronary heart disease. *Experimental biology and medicine*, 227(10), 900-907.
- Rissanen, T. H., Voutilainen, S., Nyyssönen, K., Salonen, R., Kaplan, G. A., & Salonen, J. T. (2003). Serum lycopene concentrations and carotid atherosclerosis: the Kuopio ischaemic heart disease risk factor study. *The American journal of clinical nutrition*, 77(1), 133-138.
- Santos-Cervantes, M. E., Ibarra-Zazueta, M. E., Loarca-Piña, G., Paredes-López, O., & Delgado-Vargas, F. (2007). Antioxidant and antimutagenic activities of *Randia echinocarpa* fruit. *Plant Foods for Human Nutrition*, 62(2), 71-77.
- Seeram, N. P. (2008). Berry fruits for cancer prevention: current status and future prospects. *Journal of agricultural and food chemistry*, 56(3), 630-635.
- Sesso, H. D., Liu, S., Gaziano, J. M., & Buring, J. E. (2003). Dietary lycopene, tomato-based food products and cardiovascular disease in women. *The Journal of Nutrition*, 133(7), 2336-2341.



- Shmueli, H., Burger, O., Neeman, I., Yahav, J., Samra, Z., Niv, Y., Sharon, N., Weiss, E., Athamna, A., & Tabak, M. (2004). Susceptibility of *Helicobacter pylori* isolates to the antiadhesion activity of a high-molecular-weight constituent of cranberry. *Diagnostic microbiology and infectious disease*, 50(4), 231-235.
- Siemensma, A. (1996). Natural mixed carotenoids and supplementation of foods. *Quest International: Bussum, The Netherlands*.
- Soto-Zamora, G., Yahia, E. M., Brecht, J. K., & Gardea, A. (2005). Effects of postharvest hot air treatments on the quality and antioxidant levels in tomato fruit. *LWT-Food Science and Technology*, 38(6), 657-663.
- Stapleton, P. A., James, M. E., Goodwill, A. G., & Frisbee, J. C. (2008). Obesity and vascular dysfunction. *Pathophysiology*, 15(2), 79-89.
- Stewart, A. J., Bozonnet, S., Mullen, W., Jenkins, G. I., Lean, M. E., & Crozier, A. (2000). Occurrence of flavonols in tomatoes and tomato-based products. *Journal of agricultural and food chemistry*, 48(7), 2663-2669.
- Subhash, K., Bose, C., & Agrawal, B. (2007). Effect of short term supplementation of tomatoes on antioxidant enzymes and lipid peroxidation in type-II diabetes. *Indian Journal of Clinical Biochemistry*, 22(1), 95-98.
- Timlin, M. T., & Pereira, M. A. (2007). Breakfast frequency and quality in the etiology of adult obesity and chronic diseases. *Nutrition reviews*, 65(6), 268-281.
- Tonucci, L. H., Holden, J. M., Beecher, G. R., Khachik, F., Davis, C. S., & Mulokozi, G. (1995). Carotenoid content of thermally processed tomato-based food products. *Journal of agricultural and food chemistry*, 43(3), 579-586.
- Traber, M. G., & Atkinson, J. (2007). Vitamin E, antioxidant and nothing more. *Free Radical Biology and Medicine*, 43(1), 4-15.
- Tyssandier, V., Feillet-Coudray, C., Caris-Veyrat, C., Guillard, J.-C., Coudray, C., Bureau, S., Reich, M., Amiot-Carlin, M.-J., Bouteloup-Demange, C., & Boirie, Y. (2004). Effect of tomato product consumption on the plasma status of antioxidant microconstituents and on the plasma total antioxidant capacity in healthy subjects. *Journal of the American College of Nutrition*, 23(2), 148-156.
- Van Eenwyk, J., Davis, F. G., & Bowen, P. E. (1991). Dietary and serum carotenoids and cervical intraepithelial neoplasia. *International journal of cancer*, 48(1), 34-38.
- Vaya, J., Mahmood, S., Goldblum, A., Aviram, M., Volkova, N., Shaalan, A., Musa, R., & Tamir, S. (2003). Inhibition of LDL oxidation by flavonoids in relation to their structure and calculated enthalpy. *Phytochemistry*, 62(1), 89-99.
- Vrieling, A., Verhage, B. A., Van Duijnhoven, F. J., Jenab, M., Overvad, K., Tjønneland, A., Olsen, A., Clavel-Chapelon, F., Boutron-Ruault, M. C., & Kaaks, R. (2009). Fruit and vegetable consumption and pancreatic cancer risk in the European Prospective Investigation into Cancer and Nutrition. *International journal of cancer*, 124(8), 1926-1934.
- Weisburger, J. H. (1998). Evaluation of the evidence on the role of tomato products in disease prevention. *Proceedings of the Society for Experimental Biology and Medicine*, 218(2), 140-143.
- Willcox, J. K., Catignani, G. L., & Lazarus, S. (2003). Tomatoes and cardiovascular health.
- Winterbourn, C. C. (2008). Reconciling the chemistry and biology of reactive oxygen species. *Nature chemical biology*, 4(5), 278-286.
- Witztum, J. L. (1994). The oxidation hypothesis of atherosclerosis. *The Lancet*, 344(8925), 793-795.
- Woodall, A. A., Lee, S. W.-M., Weesie, R. J., Jackson, M. J., & Britton, G. (1997). Oxidation of carotenoids by free radicals: relationship between structure and reactivity. *Biochimica et Biophysica Acta (BBA)-General Subjects*, 1336(1), 33-42.
- YILMAZ, E. (2001). The chemistry of fresh tomato flavor. *Turkish Journal of Agriculture and Forestry*, 25(3), 149-155.
- Zaman, A., Helft, G., Worthley, S., & Badimon, J. (2000). The role of plaque rupture and thrombosis in coronary artery disease. *Atherosclerosis*, 149(2), 251-266.
- Zhang, S., Tang, G., Russell, R. M., Mayzel, K. A., Stampfer, M. J., Willett, W. C., & Hunter, D. J. (1997). Measurement of retinoids and carotenoids in breast adipose tissue and a comparison of concentrations in breast cancer cases and control subjects. *The American journal of clinical nutrition*, 66(3), 626-632.
- Zhao, Z., & Moghadasian, M. H. (2008). Chemistry, natural sources, dietary intake and pharmacokinetic properties of ferulic acid: A review. *Food chemistry*, 109(4), 691-702.