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Perspective

# A Global Health Preventive Medicine Overture: Lycopene as an Anticancer and Carcinopreventive Agent in the Deterrence of Cervical Cancer *Liking Lycopene*

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**Abbreviations** AICR: American Institute for Cancer Research; GJC: Gap Junctional Communication; ROS: Reactive Oxygen Species

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## Abstract

Cervical cancer is a global healthcare concern for all women; it respects no geographical boundaries. Cervical cancer involves substantial costs not only in treatment but also in productivity lost. Prevention and screening programs have helped slow the rising incidence of cervical cancer, but more needs to be done. Preventive measures by way of diet should be considered. Certain familiar natural food sources, especially the tomato, contain in abundance a bioactive compound, lycopene. Lycopene is a lipid-soluble compound, and constitutes more than 80% of total tomato carotenoids in fully red-ripe fruits [1]. Lycopene has demonstrated potent antioxidant properties as well as chemopreventive and anticancer properties [2]. Lycopene, being adequate and bioavailable in the tomato's raw form, becomes enhanced and more bioactive when heated as in cooking. Adverse effects of lycopene are rare; in an overdose (or an allergic reaction) any adverse effects are easily reversible. The potential benefits and lack of adverse effects bode well for taking the next step in proposing research into using natural sources of lycopene, such as the tomato, on a global basis for preventing and reducing the incidence of cervical cancer.

## Preface

- "Let your food be your medicine and your medicine be your food...". Hippocrates
- "The plant is a complex organism. It is the result of the biological evolution over a period of hundreds of millions of years. Vitamins and other substances contained in the plants are tens of thousands. These are responsible for the right functioning of the complex human biochemistry and human genome (DNA) …" [3].

## Introduction

Cervical cancer is the fourth most common cancer among women. In 2012, there were an estimated 528,000 new cases and 266,000 deaths from cervical cancer worldwide accounting for 7.5% of all female cancer deaths [4]. Treatment for cervical cancer is complex and can include surgery, chemotherapy, and radiation therapy. The associated costs of cervical cancer are extreme, not just in the cost of treatment but also in work rate. In the U.S., alone, the cost of cancer of the cervix was reported as follows (in USD): initial: 45,174; continuing:1,425; last year of life (cancer death): 78,553; (other causes): 7,949 [5].

### Anticarcinogenic Properties of Lycopene

Lycopene has demonstrated anticarcinogenic properties which may apply to the prevention of cervical cancer. Although lycopene comes from numerous natural sources, it is found in abundance in Solanum lycopersicum, the tomato. Other natural sources of lycopene are, but not limited to, watermelon, papaya, grapefruit, asparagus, mango, and carrot [6].

It is interesting and relevant to note that, unlike carotenoids found in carrots, lycopene is not diverted to the Vitamin A pathway; it remains available to do different functions, such as acting as an anticancer agent. The anticarcinogenic properties of lycopene will be discussed in more detail along with the chemical structure and shape as they apply to the use and efficacy of lycopene in anticancer applications, in particular, the prevention of cervical cancer.

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### Enhanced Anticarcinogenic Properties of Lycopene

Unlike certain other fruits and vegetables, many of the intrinsic qualities and reparative and restorative factors of the tomato (notably lycopene) are not destroyed or rendered non-bioavailable or non-bioactive when heated and cooked; instead, the anticancer qualities of lycopene in heating and cooking are augmented and enhanced. When cooked, lycopene remains effective and becomes more bioactive (although the conformation/chirality may change). In fact, unlike other fruits and vegetables wherein nutritional content, e.g., Vitamin C is diminished upon cooking, processing of tomatoes increases the concentration of bioavailable lycopene. Lycopene in tomato paste is up to four times more bioavailable than in uncooked tomatoes [7].

This enhancement of bioavailability upon heating is significant as humans are accustomed to cooking (heating) their food, a process in which much of the intrinsic value of the food is diminished or lost. Regarding lycopene in the tomato, however, it is not. If lycopene is to be considered as "medicine" in the prevention of cervical cancer (and other malignancies), it needs to be readily available to consume and bioavailable when prepared. In the tomato, lycopene acts as an anticancer/carcinopreventive agent whether the tomato is raw or cooked suggesting that tomatoes are one of the best natural, common food sources for obtaining vital lycopene.

## Discussion

### Overture for Lycopene as a Global Public Health Proposal

It is considered material to review the fundamental pathophysiologic pathways that can result in cancer. The function of this review is to ascertain if the behavior of lycopene in the human body can, indeed, be identified for potential antagonistic effects to malignancy.

### Malignancies and Lack of Vitamins

Malignant tumors (cancer, sarcomas, leukemias, lymphomas) are caused by severe genetic mutations of the cell's DNA (chromosome aberrations). Therefore, malignant tumors are caused, in part, by chronic deficiencies in vitamins (the lack thereof does not allow for the repair of the genetic damage or the apoptosis-induced death of affected cells). Thus, the treatment of certain tumors should include the intake of high doses of vitamins to contribute to the apoptosis of tumor cells [8].

Free radicals in oxidative stress influence many carcinogens and cancers. Free radicals can damage a cell's DNA resulting in a mutated version of that cell. (Free radicals can also damage cell proteins and cell membranes.) If a mutated cell escapes or evades the host's natural defense mechanisms and trumps apoptosis, it can result in cancer. Free radicals accomplish this through a process called oxidation (aka oxidative damage)-the "stealing" of electrons.

Typically, the human body can cope with free radicals. However, during periods of overwhelming free radical development—termed, oxidative stress—the body's innate defense mechanisms may not be able to contend with and contain free radicals; damage and mutations can occur, and disease can result.

### The Role and Action of Antioxidants

Antioxidants, such as lycopene, are molecules which safely interact with free radicals and terminate the chain reaction before vital molecules are damaged. Antioxidants can decrease oxidative damage directly (by reacting with free radicals) or indirectly (by inhibiting the activity or expression of free radical generating enzymes or enhancing the activity or expression of intracellular antioxidant enzymes) [9]. In general, antioxidants can neutralize free radicals by accepting or donating electrons to eliminate the unpaired condition of the radical. Figure 1 (below) depicts the Reactive Oxygen Species (ROS) types and sources and action point of antioxidants.

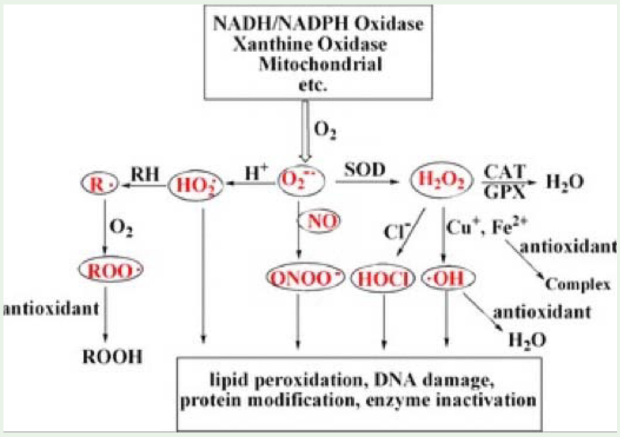


**Figure 1:** Summary of ROS types and sources, and action point of antioxidants. Note the hydroxyl (OH) free radic.

**Note:** Chemical and molecular mechanisms of antioxidants: experimental approaches and model systems **[9].**

### The Anticarcinogenic Properties of Lycopene

### Lycopene's "Vital Amine"

The lycopene's "vital amine" contributes to enhanced bioactivity in neutralizing free radicals. In the classic amine, the basic ammonia structure is changed when the hydrogen atoms are replaced by alkyl groups to form amines. The classic amine (Figure 2) has a nitrogen core. However, the term "vital amines"—which was coined by scientist Casimir Funk in 1912—was later changed to vitamins. The "e" at the end of "vitamine" was removed when it was realized that vitamins need not be nitrogen-containing amines [10].

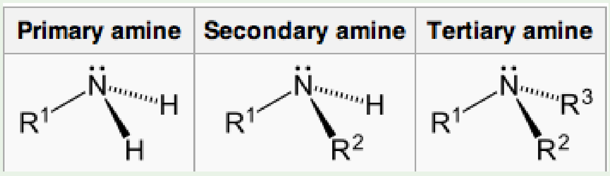


**Figure 2:** The classic amine.

**Note:** Reprinted from the public domain.

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**Lycopene as a Free Radical Antagonist (Scavenger)**

lycopene (and many other free radical antagonists) do not need nor have a classic amine chain. In the case of lycopene, several hydrogen atoms can be abstracted from lycopene by a hydroxyl radical; plus, the additional "scavenging" of an OH radical can take place at each of the various carbon atoms of lycopene with fairly low barrier energies. Lycopene has ample carbon atoms to effect this change; thus, giving lycopene an advantage over other free radical antagonists.

Scavenging free radicals is not the only capability of lycopene. Lycopene also takes part in several other pathways that lead to the elimination of free radicals, such as the conversion of free radicals to less damaging forms, the transfixing of free radicals until they can be removed by the body's natural scavenging mechanisms (before causing damage), participating in cell wall repair, and the synergistic activation of important enzymes and enzymatic reactions [11].

**Lycopene as Antioxidant**

Lycopene functions as a very potent antioxidant. Lycopene can trap singlet oxygen and reduce mutagenesis in the Ames test (a test to determine the mutagenic activity of chemicals by observing whether they cause mutations in sample bacteria).

**Lycopene and Growth Factor Receptor Signaling**

Lycopene, at physiological concentrations, can inhibit human cancer cell mutagenesis by interfering with growth factor receptor signaling and cell cycle progression specifically in prostate cancer cells without evidence of toxic effects. Kanetsky et al. (1998) reported that "lycopene . . . may play a protective role in the early stages of cervical carcinogenesis" [12].

**Lycopene and Connexin 43**

Studies using human and animal cells have identified the gene, connexin 43; connexin 43's expression is upregulated by lycopene and allows direct intercellular gap junctional communication (GJC). GJC is deficient in many human tumors and its restoration or upregulation is associated with a decreased proliferation of cancer cells [13].

**Where Lycopene Lives and Why; How this Supports Lycopene as an Anticancer Agent.**

Lycopene is the most common carotenoid in the human body and a potent carotenoid antioxidant. Lycopene is easily absorbed by the organism and is naturally present in human plasma and tissues in higher concentrations than other carotenoids. Lycopene is mainly distributed to fatty tissues and organs, such as the adrenal glands, liver, prostate, and testes. Its level in the human body is affected by several biological and lifestyle factors. Because of its lipophilic nature, lycopene concentrates in low-density and very-low-density lipoprotein fractions of the serum. However, unlike other carotenoids, lycopene levels in serum or tissues do not correlate well with overall intake of fruits and vegetables [14].

Lycopene remains at high levels in human plasma due to several factors. It tends to accumulate with fat in the body; it is a relatively large biomolecule having a high molecular weight and is, therefore, not easily filtered out and excreted from the body; and, as it is required for many essential functions and reactions in the human body, it must be readily available and is thusly stored in ample quantities.

**Could Synthesized Sources of Lycopene be as Effective as Natural Sources?**

Are manufactured, synthesized, or non-natural sources of lycopene as bioactive, or as efficacious, as an anticancer agent or anticarcinogen as lycopene derived from natural sources? According to Dr. Guiseppi Nacci:

> A plant constitutes a single therapeutic unit where the active principles from some characteristic phytocomplex, by binding themselves to or interacting with other molecules, are eliminated during the purifying processes. So, the phytocomplex is the "quintessence" of medicinal plants and not their purified "active principle". A phytocomplex could be considered as a complex biochemical element constituting the whole pharmacological unit of medicinal plants [3].

Applying this concept to lycopene, Dr. Nacci decries that it is the phytocomplex, not just the purified bioactive principle (in this case, the lycopene), that renders the functional constituents bioactive and effective. The research shows lycopene along with other nutrients, as well as those found in its parent phytocomplex, are more effective than lycopene alone.

**A Look at the Structure of Lycopene**

The following section discusses the isolated "active principle" of the tomato, the lycopene; to determine if its chemical structure and shape, alone (without its parent phytocomplex), is consistent as a carcinopreventive agent.

**The chemical characteristics of lycopene are as follows (see Figures 3-6):**

- Molecular Formula: C40H56
- Average mass: 536.873 Da
- Monoisotopic mass: 536.438232 Da
- Double-bond stereo

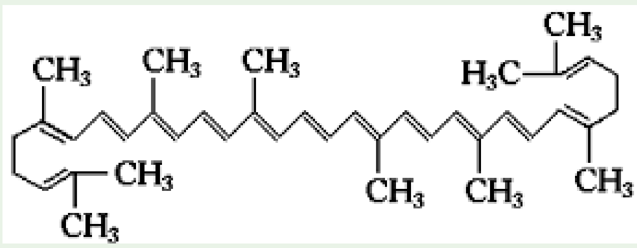


**Figure 3:** Chemical structure of lycopene.
**Note:** Reprinted from The Morning Star Company.

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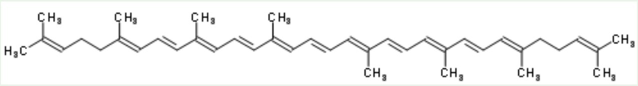

**Figure 4:** 2D structure of lycopene.

**Note:** Reprinted from ChemSpider. Search and share chemistry.

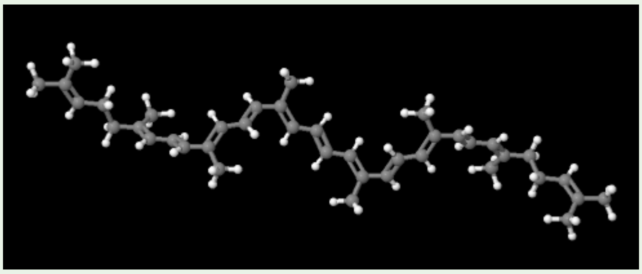

**Figure 5:** 3D structure of lycopene.

**Note:** Reprinted from ChemSpider. Search and share chemistry.

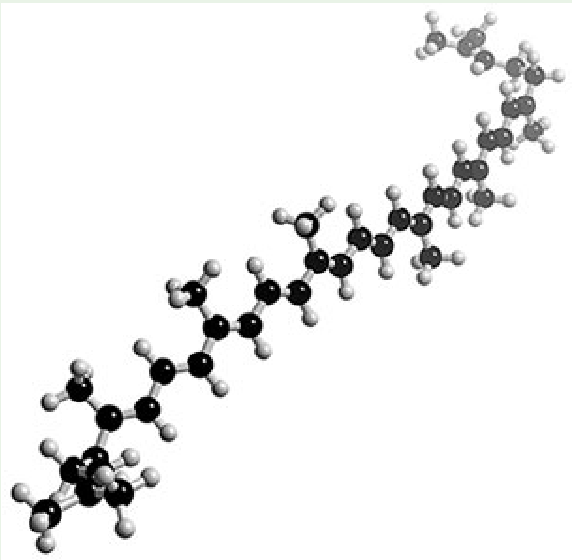

**Figure 6:** 3D version of lycopene.

**Note:** Reprinted from The Morning Star Company.

### A Comparison of the Absorption of Trans-Lycopene with Cis-Lycopene

In an American Institute for Cancer Research (AICR) report, Unlu et al. (2016) demonstrated that processing red tomatoes with oil and high heat for an extended period of time (260˚F for 40 minutes) changed the shape of some of the lycopene from trans (denoted E) to cis (denoted Z). In one study, they found that when humans consumed this cis-lycopene-rich tomato sauce, the consumption resulted in a 55 percent increase in lycopene absorption compared to the trans-lycopene-rich sauce [8]. This increased absorption is due, in part, because cis-lycopene remains more bioavailable. The corresponding structures of cis-lycopene and trans-lycopene are depicted in Figure 7 as follows.

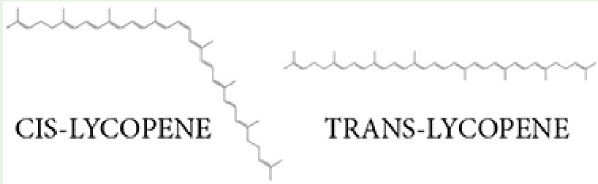


**Figure 7:** The more bio-active cis-form of lycopene (left); the comparative less bio-active trans-form of lycopene (right).

**Note:** Reprinted from AICR's Cancer Research Update. 2015.

In a separate study published in *Experimental Biology and Medicine*, researchers TW Boileau, AC Boileau and Erdman, Jr. (2002) reported:

> Lycopene, the predominant carotenoid in tomatoes, is among the major carotenoids in serum and tissues of Americans. Although about 90% of the lycopene in dietary sources is found in the linear, all-trans conformation, human tissues contain mainly cis-isomers. Several research groups have suggested that cis-isomers of lycopene are better absorbed than the all-trans form because of the shorter length of the cis-isomer, the greater solubility of cis-isomers in mixed micelles, and/or as a result of the lower tendency of cis-isomers to aggregate . . . . In vitro studies suggest that cis-isomers are more soluble in bile acid micelles and may be preferentially incorporated into chylomicrons . . . . Investigations are underway to determine whether there are biological differences between all-trans and various cis-isomers of lycopene regarding its antioxidant properties or other biological functions [15].

### Synergism with Other Nutrients Enhances Lycopene's Beneficial Actions

Most clinical trials with tomato products suggest a synergistic action of other nutrients (within the phytocomplex) with lycopene in lowering biomarkers of oxidative stress and carcinogenesis. Consumption of processed tomato products containing lycopene could, therefore, be considered a significant health benefit that can be attributed to the combination of naturally-occurring nutrients in tomatoes [16].

The statements mentioned above support a whole food, or supplemented, source of lycopene as being more effective than isolated or synthesized lycopene.

### Safety, Adverse Effects, and Limitations of Lycopene

Lycopene is widely available in natural form. It is considered "likely safe" when taken in appropriate amounts and "likely safe" in pregnancy when taken in amounts commonly found in foods. For the male patient, however, it is advised to avoid large doses of lycopene if the patient has prostate cancer, and for both men and women who have an allergy to lycopene. The known adverse effects of lycopene are minimal and, if they do occur, are reversible.

There is less consensus regarding lycopene in preventing or inhibiting breast cancer. While certain anecdotal sources proclaim lycopene as complementary in reducing the risk of breast cancer in women, Sesso et al. (2005) reported that "neither higher dietary nor plasma lycopene levels were associated with a reduced risk of breast cancer in middle-aged and older women" [17].

## Conclusion

Currently, the benefits of lycopene as an anticancer and carcinopreventive agent appear to far outweigh any risks associated with ingesting it. Research on lycopene regarding its role as an anticarcinogen in cervical cancer and other conditions continues. Most current research supports lycopene as having anticarcinogenic properties. Lycopene shows a high probability of acting as a carcinopreventive agent.

Almost all women globally—but especially those between the ages of 35-55 years of age, those who smoke, those who have experienced HPV (human papillomavirus) infection or genital herpes, and those who have taken or are currently taking oral contraceptives—may benefit from consuming ample amounts of lycopene. One of the most convenient and bioavailable sources of beneficial lycopene is the paste of Solanum lycopersicum, the tomato.

Numerous studies have demonstrated the potential of lycopene as an anticarcinogen. Supporting further research for lycopene as a carcinopreventive agent and promoting the consumption of lycopene-containing foods as a global, public health proposal seems wise and warranted.

### Conflict of Interest Statement

The author declares that this paper was written in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

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