LYCOPENE – ANTIOXIDANT WITH RADIOPROTECTIVE AND ANTICANCER PROPERTIES. A REVIEW

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ABSTRACT
Ionizing radiation may cause damage to living tissue by producing free radicals like reactive oxygen species (ROS). ROS can randomly react with lipids, proteins and nucleic acids of cell causing oxidative stress and damage in these macromolecules, leading to pathogenesis of chronic diseases and age related and also cancer. The first line of defense from the damaging effects of ROS is antioxidants, which convert the oxidants to less reactive species. Lycopene (LYC) is an acyclic isomer of beta-carotene. It synthesized by plants or autotrophic bacteria but not by animals. Red fruits and vegetables, including tomatoes, watermelons, pink grapefruits, apricots, pink guavas and papaya contain LYC. This carotenoid has very strong antioxidant properties. The many studies confirm that dietary supplementation with LYC reduces risk of cancers of many organs, but also retard the growth of the tumors. LYC has also chemopreventive effects against other diseases such as cardiovascular disease, osteoporosis, male infertility and inhibits the toxic action of other agents. Numerous in vitro and animal studies showed that LYC may provide protection against damages induced by ionizing radiation. It suggests that supplementation of LYC might be useful in diminishing of negative effect of cancer radiotherapy or in mitigating the effects of possible radiation accidents on human health.

Key words: lycopene, antioxidants, anticarcinogenic agents, radioprotection

INTRODUCTION
The term ROS (reactive oxygen species) refers to a group of molecules (such as peroxides and free radicals) derived from oxygen that are highly reactive toward biomolecules. Free radicals are any atom or molecule that contains one or more unpaired electrons. They are usually more reactive than the corresponding non-radicals because they can act as oxidizing agents. ROS are constantly generated in living organisms as byproducts of cellular metabolism, but can also be produced as a consequence of ionizing radiation (IR),...
Ionizing radiation carries sufficient energy to remove an electron from an atom or molecule. This ionization produces free radicals, atoms or molecules containing unpaired electrons, which tend to be especially chemically reactive. Damages of tissue may be caused by ionization, which disrupts molecules directly and also produces highly reactive free radicals (mainly hydroxyl radicals from water in the surrounding environment), which attack nearby cells.

The radioprotective effects of antioxidants and the mechanisms by which these effects are mediated depend on the properties of both the antioxidant and the compartment (e.g., cellular or tissue targets) where the radioprotective effects are measured.

Therefore dietary antioxidants may protect cells against DNA damage induced by endogenous and exogenous sources, including IR. The intake of antioxidants, which can neutralize reactive oxygen species (ROS) generated endogenously or exogenously, has been extensively investigated in relation to DNA damage and cancer risk [18, 27, 53, 71, 81, 92, 95]. During past decades, numerous animal or in vitro studies have suggested that antioxidants may provide protection against several forms of DNA damage induced by IR [18, 93, 99]. To present time, human data supporting these associations are limited. Of the dietary antioxidants, vitamins C and E and beta-carotene have been the focus of most research [72, 81, 90, 92, 95]. However, there are other carotenoids with antioxidant properties, such as alpha-carotene, beta-cryptoxanthin, lycopene, lutein, and zeaxanthin, which are found in relatively large amounts in the diet [27, 90]. Studies of intakes of these dietary antioxidants in IR-exposed populations are therefore needed to clarify their possible protective role.

LYCOPENE CHEMICAL STRUCTURE AND BIOAVAILABILITY

Fruits and vegetables contain in excess of 40 carotenoids that are routinely absorbed and metabolized by humans [39, 40].

Intake of tomato and tomato-based food products contributes to the absorption of a wide range of carotenoids in human serum and tissues. The prominent carotenoid in tomatoes is the red pigment lycopene, an acyclic isomer of beta-carotene, also synthetized by other plants and microorganisms but not by animals. Red fruits and vegetables, including tomatoes, watermelons, pink grapefruits, apricots, pink guavas and papaya contain lycopene [88]. But, the main sources of lycopene...
in food rations are tomato products (about 60-50%) and fresh tomatoes (about 30-40%) [33, 96, 98].

Lycopene is a highly unsaturated hydrocarbon containing 11 conjugated and 2 unconjugated double bonds. As a polycene it undergoes cis-trans isomerization induced by light, thermal energy and chemical reactions [62,106]. Lycopene is one of the most potent antioxidants, with a singlet-oxygen-quenching ability twice as high as that of beta-carotene and 10 times higher than that of alpha-tocopherol [17].

In human, serum lycopene levels significantly increase after consuming tomato foods or lycopene supplementation [69, 73]. However, not all sources of lycopene are equally bioavailable. Ingested in its natural trans form, such as is prominent in tomatoes, lycopene is poorly absorbed [70] whereas heat processing of tomatoes and tomato products induces isomerization of lycopene from all-trans to cis configuration in turn increasing its bioavailability [1, 12, 89]. In human plasma, total lycopene is an isomeric mixture containing 40% to 50% as cis isomers. The relative stabilities of the most commonly identified lycopene isomers, from most stable to least, are 5-cis, all-trans, 9-cis, 13-cis, 15-cis, 7-cis, and 11-cis. The relative antioxidant properties of these same lycopene isomers as indicated by their ionization potential from greatest to least, are 5-cis, 9-cis, 7-cis, 13-cis, 15-cis, 11-cis and all-trans [11].

Lycopene is the most predominant carotenoid in human plasma. Its level is affected by several biological and lifestyle factors [25, 71]. The elderly, people living in big cities and with higher level of educations or physical activity consume more lycopene in daily food rations [97, 98]. Owing to their lipophilic nature, lycopene and other carotenoids are found to concentrate in low-density and very-low-density lipoprotein fractions of the serum [12]. Lycopene is also found to concentrate in the adrenal gland, testes, liver and prostate gland, where it is the most prominent carotenoid [37, 63, 79, 86]. The biological activities of carotenoids such as beta-carotene are related in general to their ability to form vitamin A within the body. Since lycopene lacks the beta-ionone ring structure, it cannot form vitamin A [88]. Its biological effects in humans have therefore been attributed to mechanisms other than vitamin A.

**ANTICARCINOGENIC ACTIVITY OF LYCOPENE**

Two major hypotheses have been proposed to explain the anticarcinogenic activities of lycopene: nonoxidative and oxidative mechanisms.

Lycopene is the most potent antioxidant among various common carotenoids. Its antioxidant activity has been extensively evaluated based on its ability to scavenge free radicals in cell culture and in animal models [48]. Experimental evidence also suggests that lycopene can quench singlet oxygen (\(^{1}\text{O}_2\)), scavenge free radicals of nitrogen dioxide (\(\text{NO}_2\cdot\)), thiyl (RS\(\cdot\)) and sulphonyl (RSO\(\cdot\)). All these evidence are helpful for understanding the antioxidant role of lycopene [103].

The possible mechanisms by which carotenoids quench singlet oxygen may be the following. During singlet oxygen quenching energy is transferred from \(\text{O}_2\) to the lycopene molecule, converting it to the energy rich triplet state [100]. Trapping of other ROS, OH, NO\(_2\) or peroxynitrite, leads to oxidative breakdown of the lycopene molecule. In this way, lycopene may protect in vivo against oxidation of lipids, proteins and DNA [87].

Among the nonoxidative mechanisms, the anticarcinogenic effects of lycopene have been suggested to be due to regulation of gap-junction communication in mouse embryob fibroblast cells [107,108]. Lycopene is hypothesized to suppress carcinogen-induced phosphorylation of regulatory proteins such as p53 and Rb antioncogenes and stop cell division at the G0–G1 cell cycle phase [55]. Astorg et al. [3] proposed that lycopene-induced modulation of the liver metabolizing enzyme, cytochrome P4502E1, was the underlying mechanism of protection against carcinogen induced preneoplastic lesions in the rat liver. Preliminary in vitro evidence also indicates that lycopene reduces cellular proliferation induced by insulin-like growth factors, which are potent mitogens, in various cancer cell lines [48].

With respect to lycopene’s role in the prevention of cancer, Giovannucci [30] reviewed 72 epidemiological studies and found the consumption of tomatoes and tomato products or circulating levels of lycopene to be inversely related to risk of cancers, most prominently, cancers of the prostate gland, lung, and stomach. The results from this study, which examined case-control dietary studies, prospective dietary studies and blood specimen-based investigations, also suggested a reduced risk of other cancers, including pancreatic, colorectal, esophageal, oral, breast, and cervical cancers. Other cancers investigated did not show clear relationships to the intake of tomato, tomato products or lycopene.

The nutritional significance of lycopene has also been demonstrated in an in vivo study of colon cancer involving rodents [61]. Levy et al. [48] have shown that lycopene is more potent than \(\alpha\) and \(\beta\)-carotene in inhibiting the cell growth of various human cancer cell lines.

The pioneering work of the Karolinska group also included a thorough examination of the effects of lycopene administration on the growth of Ehrlich ascites tumour cells in mice [50]. Pretreatment with lycopene increased the time to tumour development and survival time. Injection of lycopene following the administration...
of low concentrations of tumour cells also retarded the growth of the tumours.

It was found that lycopene and beta-carotene have the capacity to inhibit breast cancer cells proliferation, arrest the cell cycle in different phases, and increase apoptosis [31]. But also alone LYC selectively inhibited MCF-7 breast cancer cells through disrupting cytoskeleton formation and thus prohibiting the progress of cell cycle and ultimately cell proliferation [94].

Other studies indicate that this carotenoid seems to be an able candidate for chemoprevention in hepatocarcinogenesis in mice resulting from N-diethyl-nitrosamine-insults and suggest the potential role of dietary LYC against the risk of ovarian cancer among postmenopausal women, which provides opportunity for developments in the prevention of ovarian cancer [32].

THE EFFECTS OF LYCOPENE AGAINST ANOTHER DISEASE

In addition to cancer and lycopene, another area of promising research is that of lycopene and cardiovascular disease (CVD). In a large multicenter case-control study (EURAMIC), the relationship between adipose tissue antioxidant status (alpha- and beta-carotene and lycopene) and acute myocardial infarction were evaluated in 662 cases and 717 controls [43]. Lycopene was found to be protective against myocardial infarction risk in non-smokers. Also related to cardiovascular disease, mildly hypercholesterolemic men and women with grade-1 hypertension taking 15 mg/day of lycopene from tomato oleoresin antioxidant-rich tomato extract had significantly decreased systolic and diastolic blood pressure compared to placebo [23].

In Sesso et al.’s work [18] higher plasma lycopene concentrations were associated with a lower risk of CVD in women. Also it found that lower plasma levels of lycopene were associated with increased risk of atherosclerotic lesions, by the presence of calcified plaques in the abdominal aorta, and with an increased risk of acute coronary events or stroke [30, 42, 60].

Recently, lycopene research has begun to explore the potential for this antioxidant carotenoid to work against the onset of bone disease. In a recent in vitro study of bone marrow prepared from rat femurs, it was demonstrated that lycopene, in the absence or presence of parathyroid hormone (PTH), inhibited osteoclastic mineral resorption and formation of tartrateresistant acid phosphatase (TRAP) positive multinucleated osteoclasts, as well as the ROS produced by osteoclasts [74]. The authors suggested that this finding may be important in the pathogenesis, treatment and prevention of osteoporosis.

Recently is also studied the impact of lycopene on male infertility. Infertile men genetically tend to produce higher levels of free radicals. Ongoing research in India is exploring this relationship and the influence of supplementing with lycopene. In one study of 50 volunteers with low active sperm counts, 35 volunteers (70%) experienced an improvement in sperm count, 30 (60%) had improved functional sperm concentrations, 27 (54%) had improved sperm motility, 23 (46%) had improved sperm motility index, and 19 (38%) had improved sperm morphology following consumption of 8 mg/day of lycopene supplementation from tomato oleoresin extract [59].

LYC has significant anti-angiogenic effects both in vitro and ex vivo [35].

In turn, the study of Li and Xu [49] suggests that lycopene supplement >12 mg/day might effectively decrease systolic blood pressure (SBP).

RADIOPROTECTIVE ABILITY OF LYCOPENE

The available reports have shown that little work has been carried out on lycopene for its radioprotective effect. Only few publications have investigated the protective effect of lycopene against ionizing radiation [2, 9, 76, 77, 83, 84]. Forsberg et al. [29] showed that lycopene administration before X-irradiation protected mice from lethal bacterial infections which killed irradiated, infected control mice. While Saada et al. [77] and Andic et al. [2] tested the protective effect of lycopene against radiation-induced intestinal toxicity. Although lycopene accumulation was lower in the small intestine than in the liver, both studies showed that lycopene has a protective effect against intestinal toxicity by reducing lipid peroxidation and increasing antioxidant enzyme activity. Srinivasan et al. [84] showed that pretreatment of lycopene to gamma-irradiated lymphocytes resulted in decrease in lipid peroxidation and improved antioxidant status preventing the damage to the lymphocytes. The protective effects of lycopene, at doses of 1.86, 9.31 and 18.62 μM, were tested in isolated rat hepatocytes cultured in vitro and irradiated with to 1.2 and 4 Gy of γ-irradiation. Concentrations levels of thiobarbituric acid reactive substance (TBARS), which indicate lipid peroxidation, were significantly decreased and GSH (glutathione) levels, GSH-Px (glutathione peroxidase), SOD (superoxide dismutase) and catalase activities were significantly increased, in lycopene groups compared with controls. In addition, a decrease by lycopene induced by gamma-radiation DNA damage by lycopene was shown using the comet assay. This may be due to the antioxidant sparing action of lycopene. In similar study of Saada et al. [76] rats were supplemented with
lycopene (5 mg/kg weight/day), by gavage, for 7 days before exposure to 7 Gy gamma irradiation. This resulted in diminishing amount of TBARS recorded for each subcellular structure in the liver of irradiated animals. The authors postulated that lycopene could play an important role in the recovery of the integrity of biological membranes of the liver after radiation injury. Also study of Meydan et al. [56] showed that the application of lycopene before abdominopelvic radiotherapy (RT) has the potential to reduce oxidative damage caused by RT in rats, by decreasing lipid peroxidation and stimulating antioxidant enzyme activities. These results also showed that continued lycopene treatment might be useful.

In turn Stahl et al. [85] observed protection against UV-induced erythema after dietary intervention. Tomato paste contains lycopene was selected as a natural dietary source providing carotenoids to protect against UV-induced erythema in humans. The ingestion of tomato paste (40 g/day, equivalent to 16 mg lycopene/day) over a period of 10 weeks led to elevated serum levels of lycopene and an increase of total carotenoids in skin. After 10 weeks of treatment, erythema formation was significantly lower in the group consuming the tomato paste than in the controls. This study demonstrates that UV-induced erythema can be ameliorated by dietary supplementation by lycopene. There were compared also the photoprotective effects of synthetic lycopene with a supplement derived from a tomato extract and a drink containing a solubilized form of the supplement [5]. With the different sources, similar amounts of lycopene (about 10 mg/day) were provided and after 12 weeks, significant increases in lycopene serum levels and total skin carotenoids were observed in all groups. Sensitivity towards UV light was determined after irradiation with a solar simulator determining the degree of erythema before and after supplementation. The protective effect was most pronounced in the groups that ingested the supplement or the drink.

Thus, lycopene seems to be a promising candidate for radioprotection of normal cells and cancer prevention as other natural antioxidant, resveratrol [20].

**PROTECTIVE ROLE OF LYCOPENE AGAINST OTHER AGENTS EFFECTS**

Experimental studies also showed that lycopene has a protective effect based on antioxidant status and lipid peroxidation, against toxicity induced by chemo-therapeutic drugs (such as adriamycin and cisplatin), which have cytotoxic effects that are similar to radiation [4,104].

Matos et al. [54] have reported that lycopene supplementation has decreased 77% of 8-oxodguo levels in ferric nitrolitriacetate (Fe-NTA)/ascorbate-treated cells. These results indicate that lycopene provided strong protection against DNA-based oxidation. Furthermore, consumption of tomato products was reported to reduce the susceptibility of lymphocyte DNA to oxidative damage [75].

Lycopene have a protective role against Aroclor 1254 -induced changes on GLUT4 (the glucose transporter protein, which plays a key role in glucose homeostasis) in the skeletal muscles of adult male rat. Aroclor 1254 is the commercial mixture of highly toxic environmental pollutant (polychlorinated biphenyls, PCBs), which causes a variety of adverse health effects through free radical generation [101].

Krishnamoorthy et al. [46] confirmed that polychlorinated biphenyls (PCBs) induced Sertoli cellular (SCs) apoptosis by both Fas Ligand and mitochondria mediated pathway, associated with increased oxidative stress. Lycopene prevented the generation of ROS thereby acting against PCBs-induced apoptosis in adult rat SCs. In conclusion, the present study showed that lycopene could provide markable protection against PCBs-induced ROS mediated apoptosis in Sertoli cells.

LYC exhibits the cardioprotective potential on iso-proterenol-induced oxidative stress and heart lysosomal damage in rats. LYC supplementation to rats was significantly ameliorates lysosomal membrane damage as well as the alterations in cardiac enzymes, lipid profile and oxidative stress markers [58].

Prakash and Kumar [67] have studied the possible nitric oxide mechanism in protective effects of lycopene against the colchicine induced cognitive impairment and mito-oxidative damage in rats. Their results suggest that lycopene exhibit a neuroprotective effect by accelerating brain anti-oxidant defense mechanisms and down regulating nitric oxide pathways. Thus, lycopene may be used as therapeutic agent in preventing complications in memory dysfunction.

LYC effectively combated oxidative damage during experimental hepatitis, induced by D-galactosamine/ lipopolysaccharide and protected antioxidant defense status of the cell. Pretreatment of lycopene also offers protection against the DNA damage and confirms the antioxidant nature of the phytonutreint against experimental hepatitis [80].

The other results suggest that lycopene prevents iron-induced oxidative stress in rats cells, proliferation and autophagy at both biochemical and histological levels due to its potent free radical scavenging and antioxidant properties [51].

The results of Qu et al. [68] suggest that lycopene affords protection against methylmercury (MeHg), which is a neurotoxin that induces neuronal degeneration in the central nervous system, and these beneficial effects of lycopene maybe attributable to its roles in preventing mitochondrial dysfunction.
Lycopene provided a protective effect against ochratoxin A-induced DNA damage in both rat kidney and liver cells [6].

In turn, the administration of lycopene might alleviate pesticide cypermethrin-induced oxidative stress in carp [105].

**SUMMARY**

Lycopene is the almost strongest antioxidant in nature. It is very common and easily available. This carotenoid has not only potent free radical scavenging properties, but also helps keeping the balance of endogenous defense system of cell. The studies confirm that dietary supplementation with LYC reduces risk of cancers of many organs, but also retard the growth of the tumours.

Besides the anticancer properties this carotenoid has health-promoting influenced against another disease, like cardiovascular disease, osteoporosis, male infertility. Lycopene counteracts oxidative damage in cells caused by many agents.

During past decades, numerous animal and *in vitro* studies have proven that LYC may provide protection against mutagenesis induced by ionizing radiation. It suggests that supplementation of LYC might be useful in diminishing of sideline effect of cancer radiotherapy.

To date, the majority of published papers showed the protective effect of lycopene when its supplementation started before irradiation. Only few studies have focused on the effects of protective action of lycopene when applied at the same time or after the start of exposure to radiation. Further studies are needed to assess the promising influence of lycopene on organism after irradiation.

If it is found that lycopene may also have repair properties after exposure to ionizing radiation it might be used in mitigating the effects of possible radiation accidents on human health.

**REFERENCES**

Lycopene – radioprotective and anticancer properties


Received: 19.08.2014
Accepted: 24.10.2014