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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*

STRESZCZENIE

Promieniowanie jonizujące może powodować uszkodzenia żywej tkanki poprzez wytwarzanie wolnych rodników takich jak reaktywne formy tlenu (RFT). RFT mogą przypadkowo wchodzić w reakcję z lipidami, białkami lub kwasami nukleinowymi komórki, powodując stres oksydacyjny i uszkodzenia w tych makrocząsteczkach, co prowadzi do patogenezy chorób przewlekłych i związanych z wiekiem, a także do zachorowania na raka. Pierwsza linia obrony przed szkodliwym działaniem RFT to przeciwutleniacze, które przekształcają utleniacze do form mniej reaktywnych. Likopen (LYC) jest acyklicznym izomerem *beta*-karotenu. Jest on syntetyzowany przez rośliny i bakterie autotroficzne, ale nie przez zwierzęta. Czerwone owoce i warzywa, w tym pomidory, arbuzy, różowe grejpfruty, morele, papaja i różowe guawy zawierają LYC. Ten karotenoid ma bardzo silne właściwości antyoksydacyjne. Liczne badania potwierdzają, że suplementacja LYC zmniejsza ryzyko raka wielu narządów, a także opóźnia wzrost guza. LYC ma działanie zapobiegawcze również przeciwko innym chorobom, takim jak choroby układu krążenia, osteoporoza, niepłodność, oraz hamuje toksyczne działanie innych czynników. Badania *in vitro* i nad zwierzętami wykazały, że LYC może zapewnić ochronę przed uszkodzeniami indukowanymi przez promieniowanie jonizujące. Sugeruje to, że suplementacja LYC może być przydatna w zmniejszaniu negatywnego wpływu radioterapii na zdrowie człowieka lub w łagodzeniu skutków ewentualnych wypadków radiacyjnych.

Słowa kluczowe: *likopen, przeciwutleniacze, czynniki przeciwnowotworowe, ochrona przed promieniowaniem*

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),

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chemotherapeutic drugs and environmental exposure to transition metals and chemical oxidants [7, 24, 41, 44, 102]. ROS can randomly react with lipids, proteins and nucleic acids causing oxidative stress and damage in these macromolecules, leading to pathogenesis of age related and chronic diseases including cancer [10, 13, 26, 28, 38, 45, 52, 91].

ROS generate a variety of DNA lesions, including oxidized DNA bases, abasic sites, single-strand breaks and double-strand breaks [47]. There are 100 types of oxidative base modifications in mammalian DNA [16, 19]. Oxidative damage to DNA may lead to mutations that activate oncogenes or inactivate tumor suppressor genes [21, 41]. Many DNA repair pathways, as well as other cellular stress response pathways, such as cell cycle arrest and apoptosis, determine the probability of genetic alterations turning into neoplastic events. Specific DNA lesions have been strongly implicated in tumorigenesis [14, 15, 36, 38].

The first line of defense from the damaging effects of ROS is antioxidants, which convert the oxidants to less reactive species [82]. Antioxidants have been studied for their capacity to reduce the cytotoxic effects of radiation in normal tissues for at least 50 years [64].

To maintain the redox balance and to protect themselves from free radicals action the living cells have evolved an endogenous antioxidant defense mechanism which includes nonenzymatic entities like glutathione, ascorbic acid and enzymes like catalase, superoxide dismutase and glutathione peroxidase [57]. However, radiation exposure alters the balance of endogenous defense system [78]. Antioxidant molecules are synthesized by organisms, but larger amounts of them come from food sources. A number of dietary antioxidants have been reported to decrease free radical attack on biomolecules [22].

Ionizing radiation is dangerous for all living organisms in direct exposure. It comes from natural and artificial sources. Natural background radiation comes from five primary sources: cosmic radiation, solar radiation, external terrestrial sources, radiation in the human body and radon. IR from man-made sources like radioactive materials, X-ray tubes, and particle accelerators has many uses, including killing cancerous cells and power generation. There are several occupations, where people are exposed to radiation e.g. airline crew (the most exposed population), industrial radiography, medical radiology and nuclear medicine staff [65, 66], uranium mining workers, nuclear power plant and nuclear fuel reprocessing plant workers and research laboratories employees. However, exposure to radiation causes damage to living tissue, and can result in mutation, cancer and death [8]. The data on the associations between ionizing radiation exposure and the development of cancer are based mostly on studies of populations exposed to relatively high levels of ionizing radiation, such as Japanese atomic bomb survivors, and recipients of selected diagnostic or therapeutic medical procedures.

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, 72, 81, 90, 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 polyene 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 β-carotene are related in general to their ability to form vitamin A within the body. Since lycopene lacks the β-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 ($^1O_2$), scavenge free radicals of nitrogen dioxide (NO_2•), thiyl (RS•) and sulphonyl (RSO_2•). 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 $^1O_2$ 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 embryo 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 α- and β-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-diethylnitrosamine-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]. *Forssberg* 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* at 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 chemotherapeutic 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 nitrilotriacetate (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, PBS), 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 isoproterenol-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 confirms 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

1. *Agarwal A., Shen H., Agarwal S., Rao A.V.*: Lycopene content of tomato products: its stability, bioavailability and in vivo antioxidant properties. J Med Food. 2001;4: 9-15.
2. *Andic F, .Garipagaoglu M., Yurdakonar E., Tuncel N., Kucuk O.:* Lycopene in the prevention of gastrointestinal toxicity of radiotherapy. Nutr Cancer. 2009; 61: 784-88.
3. *Astorg P., Gradelet S., Berges R., Suschetet M.*: Dietary lycopene decreases the initiation of liver preneoplastic foci by diethylnitrosamine in the rat. Nutr Cancer. 1997; 29(1): 60-8.
4. *Atessahin A., Yilmaz S., Karahan I., Ceribasi A.O., Karaoglu A.:* Effects of lycopene against cisplatin-induced nephrotoxicity and oxidative stress in rats. Toxicology. 2005; 212: 116-23.
5. *Aust O., Stahl W., Sies H., Tronnier H., Heinrich U.*: Supplementation with tomato-based products increases lycopene, phytofluene and phytoene levels in human serum and protects against UV-lightinduced erythema. Internat J Vit Nutr Res. 2005; 75(1): 54-60.
6. *Aydin S., Palabiyik S.S., Erkekoglu P., Sahin G., Basaran N., Giray B.K.:* The carotenoid lycopene protects rats against DNA damage induced by Ochratoxin A. Toxicon. 2013; 73: 96-103.
7. *Burnham J.:* Radiation Protection (Green Book). Chapter 4 - Biological Effects of Radiation, New Brunswick Power Corporation, 2001; 87-108.
8. *Camphausen K.A., Lawrence R.C.*: Principles of Radiation Therapy. in Pazdur R., Wagman L.D., Camphausen K.A., Hoskins W.J. (Eds) Cancer Management: A Multidisciplinary Approach. 11 ed. 2008.
9. *Cavusoglu K., Yalcin E.*: Radioprotective effect of lycopene on chromosomal aberrations (CAs) induced by gamma radiation in human lymphocytes. J Environ Biol. 2009; 30: 113-17.
10. *Chakravarti B., Chakravarti D.N.*: Oxidative modification of proteins: age-related changes. Gerontology. 2007; 53: 128–139.
11. *Chasse G.A., Mak M.L., Deretey E., Farkas I., Torday L.L., Papp J.G., Sarma D.S.R., Agarwal A., Chakravarthi S., Agarwal S., Rao A.V.:* An ab initio computational study on selected lycopene isomers. J Mol Struc: Theochem. 2001; 571: 27-37.
12. *Clinton S.K.*: Lycopene: chemistry, biology, and implications for human health and disease. Nutr Rev. 1998;56: 35-51.
13. *Cooke M.S., Evans M.D., Dizdaroglu M., Lunec J.*: Oxidative DNA damage: mechanisms, mutation, and disease. FASEB J. 2003; 17: 1195–1214.
14. *Cooke M.S., Lunec J., Evans M.D.*: Progress in the analysis of urinary oxidative DNA damage. Free Radic Biol Med. 2002; 33: 1601-14.
15. *Cooke M.S., Rozalski R., Dove R., Gackowski D., Siomek A., Evans M.D., Olinski R.:* Evidence for attenuated cellular 8-oxo-7,8-dihydro-2'-deoxyguanosine removal in cancer patients. Biol Chem. 2006; 387: 393–400.
16. *Croteau D.L., Bohr V.A.*: Repair of oxidative damage to nuclear and mitochondrial DNA in mammalian cells. J Biol Chem. 1997; 272: 25409-12.
17. *Di Mascio P., Kaiser S., Sies H.*: Lycopene as the most effective biological carotenoid singlet oxygen quencher. Arch Biochem Biophys. 1989; 274: 532-8.
18. *Diplock A.T., Charleux J.L., Crozier-Willi G., Kok F.J., Rice-Evans C., Roberfroid M., Stahl W., Vina-Ribes J.:* Functional food science and defense against reactive oxidative species. Br J Nutr. 1998; 80 (suppl 1): S77-112.
19. *Dizdaroglu M.:* Chemical determination of free radical--induced damage to DNA. Free Radic Biol Med. 1991, 10: 225–242.

20. *Dobrzyńska M.M.:* Resveratrol as promising natural radioprotector. A review. Rocz Panstw Zakl Hig 2013; 64(4): 255-62.
21. *Dreher D., Junod A.F.*: Role of oxygen free radicals in cancer development. Eur J Cancer. 1996; 32A: 30–38.
22. *El-Habit O.H.M., Saada H.N., Azab K.H.S.H., Abdel-Rahman M., El-Malah D.F.:* The modifying effect of β-carotene on gamma radiation induced elevation of oxidative reactions and genotoxicity in male rats. Mutat Res. 2000; 466: 179-86.
23. *Englehard Y.N., Gazer B., Paran E.*: Natural antioxidants from tomato extract reduce blood pressure in patients with grade-1 hypertension: a double-blind, placebo-controlled pilot study. Am Heart J. 2006; 151: 100.e1-100.e6.
24. *Ercal N., Gurer-Orhan H., Aykin-Burns N.:* Toxic metals and oxidative stress part I: mechanisms involved in metal-induced oxidative damage. Curr Top Med Chem. 2001; 1: 529–539.
25. *Erdman J.W., Bierer T.L., Gugger E.T.:* Absorption and transport of carotenoids. Ann N Y Acad Sci. 1993; 691: 76-85.
26. *Evans M.D., Dizdaroglu M., Cooke M.S.*: Oxidative DNA damage and disease: induction, repair and significance. Mutat Res. 2004; 567: 1–61.
27. *Fang Y.Z., Yang S., Wu G.:* Free radicals, antioxidants, and nutrition. Nutr 2002; 18: 872-9.
28. *Filipcik P., Cente M., Ferencik M., Hulin I., Novak M.:* The role of oxidative stress in the pathogenesis of Alzheimer's disease. Bratisl Lek Listy. 2006; 107: 384–394.
29. *Forssberg A., Lingen C., Ernster L., Lindberg 0.*: Modification of the X-irradiation syndrome by lycopene. Exp Cell Res. 1959; 16: 7-14.
30. *Giovannucci E.*: Tomatoes, tomato-based products, lycopene, and cancer: review of the epidemiologic literature. J Natl Cancer Inst. 1999; 91(4): 317-31.
31. *Gloria N.F., Soares N., Brand C., Oliveira F.L., Borojevic R., Teodoro A. J.:* Lycopene and beta-carotene induce cell-cycle arrest and apoptosis in human breast cancer cell lines. Anticancer Res. 2014; 34(3):1377-86.
32. *Gupta P., Bansal M.P., Koul A.:* Spectroscopic characterization of lycopene extracts from *Lycopersicum esculentum* (Tomato) and its evaluation as a chemopreventive agent against experimental hepatocarcinogenesis in mice. Phytother Res. 2013; 27(3): 448-56.
33. *Hamułka J., Wawrzyniak A., Sulich A.*: The assessment of beta-carotene, lycopene and lutein intake by selected group of adults. Rocz Panstw Zakl Hig 2012; 63(2): 179-186 (in Polish).
34. *Hosseinimehr S.J.:* Trends in the development of radioprotective agents. A review. Drug Discov Today. 2007; 12: 794-805.
35. *Huang C.S., Chuang C.H., Lo T.F., Hu M.L.:* Anti-angiogenic effects of lycopene through immunomodulation of cytokine secretion in human peripheral blood mononuclear cells. J Nutr Biochem. 2013; 24(2): 428-34.
36. *Jungst C., Cheng B., Gehrke R., Schmitz V., Nischalke H.D., Ramakers J., Schramel P., Schirmacher P., Sauerbruch T., Caselmann W.H.:* Oxidative damage is increased in human liver tissue adjacent to hepatocellular carcinoma 2. Hepatology. 2004; 39: 1663-72.
37. *Kaplan L.A., Lau J.M., Stein E.A.*: Carotenoid composition, concentrations and relationships in various human organs. Clin Physiol Biochem. 1990; 8(1): 1-10.
38. *Karihtala P., Soini Y.:* Reactive oxygen species and antioxidant mechanisms in human tissues and their relation to malignancies. APMIS. 2007; 115: 81–103.
39. *Khachik F., Beecher G.R., Goli M.B., Lusby W.R.*: Separation and quantification of carotenoids in foods. In: Packer L, Ed. Methods in Enzymology. New York: Academic Press, 1992; Vol 213, Part A: pp347-59.
40. *Khachik F., Beecher G.R., Goli M.B., Lusby W.R.:* Separation, identification, and quantification of carotenoids in fruits, vegetables and human plasma by high performance liquid chromatography. Pure Appl Chem. 1991; 63: 71-80.
41. *Klaunig J.E., Kamendulis L.M.:* The role of oxidative stress in carcinogenesis. Annu Rev Pharmacol Toxicol. 2004; 44: 239–267.
42. *Kobayashi T., Iijima K., Mitamura T., Toriizuka K., Cyong J.C., Nagasawa H.:* Effects of lycopene, a carotenoid, on intrathymic T cell differentiation and peripheral CD4/CD8 ratio in a high mammary tumor strain of SHN retired mice. Anticancer Drugs. 1996; 7: 195-8.
43. *Kohlmeir L., Kark J.D., Gomez-Gracia E., Martin B.C., Steck S.E., Kardinaal A.F., Ringstad J., Thamm M., Masaev V., Riemersma R., Martin-Moreno J.M., Huttunen J.K., Kok F.J.:* Lycopene and myocardial infarction risk in the EURAMIC Study. Am J Epidemiol. 1997; 146(8): 618-26.
44. *Kovacic P., Osuna J.A. Jr.*: Mechanisms of anti-cancer agents: emphasis on oxidative stress and electron transfer. Curr Pharm Des. 2000; 6: 277–309.
45. *Kregel K.C., Zhang H.J.*: An integrated view of oxidative stress in aging: basic mechanisms, functional effects, and pathological considerations. Am J Physiol Regul Integr Comp Physiol. 2007; 292: R18–36.
46. *Krishnamoorthy G., Selvakumar K., Venkataraman P., Elumalai P., Arunakaran J.:* Lycopene supplementation prevents reactive oxygen species mediated apoptosis in Sertoli cells of adult albino rats exposed to polychlorinated biphenyls. Interdiscip Toxicol. 2013; 6(2): 83-92.
47. *Krokan H.E., Standal R., Slupphaug G.*: DNA glycosylases in the base excision repair of DNA. Biochem J. 1997; 325: 1–16.
48. *Levy J., Bosin E., Feldmen B., Giat Y., Miinster A., Danilenko M., Sharoni Y.:* Lycopene is a more potent inhibitor of human cancer cell proliferation than either α carotene or β-carotene. Nutr Cancer. 1995; 24: 257-66.
49. *Li X., Xu J.:* Lycopene supplement and blood pressure: an updated meta-analysis of intervention trials. Nutrients. 2013; 5(9): 3696-712.
50. *Lingen C., Ernster L., Lindberg 0.*: The promoting effect of lycopene on the non-specific resistance of animals. Exp Cell Res. 1959; 16: 384-93.
51. *Liu C., Wang R., Zhang B., Hu C., Zhang H.:* Protective effects of lycopene on oxidative stress, proliferation and autophagy in iron supplementation rats. Biol Res. 2013; 46(2): 189-200.

52. *Lyras L., Perry R.H., Perry E.K., Ince P.G., Jenner A., Jenner P., Halliwell B.:* Oxidative damage to proteins, lipids, and DNA in cortical brain regions from patients with dementia with Lewy bodies. J Neurochem. 1998; 71: 302–312.
53. *Machlin L.J., Bendich A:*. Free radical tissue damage: protective role of antioxidant nutrients. FASEB J. 1987; 1: 441-5.
54. *Matos H.R., Capelozzi V.L., Gomes O.F., Mascio P.D., Medeiros M.H.G.*: Lycopene inhibits DNA damage and liver necrosis in rats treated with ferric nitrilotriacetate. Arch Biochem Biophys. 2001; 396: 171-77.
55. *Matsushima N.R., Shidoji Y., Nishiwaki S., Yamada T., Moriwaki H., Muto Y.*: Suppression by carotenoids of microcystin-induced morphological changes in mouse hepatocytes. Lipids. 1995; 30: 1029-34.
56. *Meydan D., Gursel B., Bilgici B., Can B., Ozbek N.*: Protective effect of lycopene against radiation-induced hepatic toxicity in rats. J Int Med Res. 2011; 39(4): 1239-52.
57. *Mittal A., Pathani V., Agrawala P.K., Prasad J., Singh S., Goel H.C.:* Influence of podophyllum hexandrum on endogenous antioxidant defense system in mice: possible role in radioprotection. J Ethnopharmacol. 2001; 76: 253-62.
58. *Mohamadin A.M., Elberry A.A., Mariee A.D., Morsy G.M., Al-Abbasy F.A.:* Lycopene attenuates oxidative stress and heart lysosomal damage in isoproterenol induced cardiotoxicity in rats: A biochemical study. Pathophysiology. 2012; 19(2): 121-30.
59. *Mohanty N.K., Sujit K., Jha A.K., Arora R.P.*: Management of idiopathic oligoasthenospermia with lycopene. Ind J Urol. 2001; 18(1): 57-61.
60. *Nagasawa H., Mitamura T., Sakamoto S., Yamamoto K.*: Effects of lycopene on spontaneous mammary tumour development in SHN virgin mice. Anticancer Res. 1995; 15: 1173-8.
61. *Narisawa T., Fukaura Y., Hasebe M., Ito M., Aizawa R., Murakoshi M., Uemura S., Khachik F., Nishino H.*: Inhibitory effects of natural carotenoids, -carotene, -carotene, lycopene and lutein on colonic aberrant crypt foci formation in rats. Cancer Lett. 1996; 107: 137-42.
62. *Nguyen M.L., Schwartz S.J.*: Lycopene: chemical and biological properties. Food Technol. 1999; 53: 38-45.
63. *Nierenberg D.W., Nann S.L.*: A method for determining concentrations of retinol, tocopherol, and five carotenoids in human plasma and tissue samples. Am J Clin Nutr. 1992; 56: 417-26.
64. *Okunieff P., Swarts S., Keng P., Sun W., Wang W., Kim J., Yang S., Zhang H., Liu C., Williams J. P., Huser A. K., Zhang L.:* Antioxidants reduce consequences of radiation exposure. Adv Exp Med Biol. 2008; 614: 165-78.
65. *Pattison J.E., Bachmann D.J., Beddoe A.H.*: Gamma Dosimetry at Surfaces of Cylindrical Containers. J Radiol Prot. 1996; 16(4): 249-61.
66. *Pattison J.E.*: Finger Doses Received during Samarium-153 Injections. Health Phys. 1999; 77(5): 530-35.
67. *Prakash A., Kumar A.:* Lycopene protects against memory impairment and mito-oxidative damage induced by colchicine in rats: An evidence of nitric oxide signaling. Eur J Pharmacol. 2013; 721(1-3): 373-81.
68. *Qu M., Nan X., Gao Z., Liu B., Chen Z.:* Protective effects of lycopene against methylmercury-induced neurotoxicity in cultured rat cerebellar granule neurons. Brain Res. 2013; 1540: 92-102.
69. *Rao A.V., Agarwal S.*: Bioavailability and in vivo antioxidant properties of lycopene from tomato products and their possible role in the prevention of cancer. Nutr Cancer. 1998; 31: 199-203.
70. *Rao A.V., Agarwal S.*: Role of antioxidant lycopene in cancerand heart disease. J Am Coll Nutr. 2000; 19: 563-69.
71. *Rao A.V., Agarwal S.*: Role of lycopene as antioxidant carotenoid in the prevention of chronic diseases: a review. Nutr Res. 1999; 19: 305-23.
72. *Rao A.V., Rao L.G.:* Carotenoids and human health. Pharmacol Res. 2007; 55: 207-16.
73. *Rao A.V.*: Processed tomato products as a source of dietary lycopene: bioavailability and antioxidant properties. Can J Diet Prac Res. 2004; 65: 161-65.
74. *Rao L.G., Krishnadev N., Banasikowska K., Rao A.V.*: Lycopene I-effect on osteoclasts: lycopene inhibits basal and parathyroid hormone-stimulated osteoclast formation and mineral resorption mediated by reactive oxygen species in rat bone marrow cultures. J Med Food. 2003; 6: 69-78.
75. *Riso P., Pinder A., Santangelo A., Porini M.*: Does tomato consumption effectively increase the resistance of lymphocyte DNA to oxidative damage? Am J Clin Nutr. 1999; 69: 712-18.
76. *Saada H.N., Azab Khaled S.*: Role of lycopene in recovery of radiation induced injury tomammalian cellular organelles. Pharmazie. 2001; 56: 239-41.
77. *Saada H.N., Rezk R.G., Eltahawy N.A.*: Lycopene protects the structure of the small intestine against gamma-radiation-induced oxidative stress. Phytother Res. 2010; 24(suppl 2): S204-S208.
78. *Samarth R.M., Kumar A.:* Mentha Piperia leaf extract provides protection against radiation induced chromosomal damage in bone marrow of mice. Indian J Exp Biol. 2003; 41: 229-37.
79. *Schmitz H.H., Poor C.L., Wellman R.B., Erdman J.W. Jr.*: Concentrations of selected carotenoids and vitamin A in human liver, kidney and lung tissue. J Nutr. 1991; 121: 1613-21.
80. *Sheik Abdulazeez S.*, *Thiruvengadam D.*: Effect of lycopene on oxidative stress induced during D-galactosamine/lipopolysaccharide-sensitized liver injury in rats. Pharm Biol. 2013; 51(12): 1592-9.
81. *Sies H., Stahl W., Sundquist A.R.*: Antioxidant functions of vitamins. Vitamins E and C, beta-carotene, and other carotenoids. Ann N Y Acad Sci. 1992; 669: 7-20.
82. *Sies H.:* Oxidative stress: oxidants and antioxidants. Exp Physiol. 1997, 82: 291–295.
83. *Srinivasan M., Devipriya N., Kalpana K.B., Menon V.P.:* Lycopene: an antioxidant and radioprotector against γ-radiation-induced cellular damages in cultured human lymphocytes. Toxicology. 2009; 262(1): 43-9.

84. *Srinivasan M., Sudheer A.R., Pillai K.R., Kumar P.R., Suhakaran P.R., Menon V.P.:* Lycopene as a natural protector against γ- radiation induced DNA damage, lipid peroxidation and antioxidant status in primary culture of isolated rat hepatocytes in vitro. Biochim Biophys Acta. 2007; 1770: 659-65.
85. *Stahl W., Heinrich U., Wiseman S., Eichler O., Sies H., Tronnier H.*: Dietary tomato paste protects against ultraviolet light-induced erythema in humans. J. Nutr. 2001; 131: 1449-51.
86. *Stahl W., Schwarz W., Sundquist A.R., Sies H.*: „*Cis-trans* isomers of lycopene and beta-carotene in human serum and tissues. Arch Biochem Biophys. 1992; 294: 173-77.
87. *Stahl W., Sies H.*: Antioxidant activity of carotenoids. Mol. Aspects Med. 2003; 24: 345-51.
88. *Stahl W., Sies H.*: Lycopene: a biologically important carotenoid for humans? Arch Biochem Biophys. 1996; 336: 1-9.
89. *Stahl W., Sies H.*: Uptake of lycopene and its geometrical isomers is greater from heat-processed than from unprocessedtomato juice in humans. J Nutr. 1992; 122: 2161-66.
90. *Tapiero H., Townsend D.M., Tew K.D.:* The role of carotenoids in the prevention of human pathologies. Biomed Pharmacother. 2004; 58: 100-10.
91. *Thomson A., Hemphill D., Jeejeebhoy K.N.*: Oxidative stress and antioxidants in intestinal disease. Dig Dis. 1998; 16: 152–158.
92. *Traber M.G., Atkinson J.*: Vitamin E, antioxidant and nothing more. Free Radic Biol Med. 2007; 43: 4-15.
93. *Turner N.D., Braby L.A., Ford J., Lupton J.R.*: Opportunities for nutritional amelioration of radiation-induced cellular damage. Nutrition. 2002; 18: 904-12.
94. *Uppala P.T., Dissmore T., Lau B.H., Andacht T., Rajaram S.:* Selective inhibition of cell proliferation by lycopene in MCF-7 breast cancer cells *in vitro*: a proteomic analysis. Phytother Res. 2013; 27(4): 595-601.
95. *Valko M., Izakovic M., Mazur M., Rhodes C.J., Telser J.:* Role of oxygen radicals in DNA damage and cancer incidence. Mol Cell Biochem. 2004; 266: 37-56
96. *Wawrzyniak A., Hamułka J.*: Comparative assessment of carotenoids intake by food frequency questionnaire and 4-day dietary food records method. Rocz Panstw Zakl Hig 2009, 60(1): 25-29 (in Polish).
97. *Wawrzyniak A., Sitek A.*: The influence of selected lifestyle factors on lycopene intake by women. Rocz Panstw Zakl Hig 2010; 61(3): 265-268 (in Polish).
98. *Wawrzyniak A., Sitek A.*: Lycopene intake by different aged women groups. Rocz Panstw Zakl Hig 2010; 61(2): 159-164 (in Polish).
99. *Weiss J.F., Landauer M.R.:* Radioprotection by antioxidants. Ann N Y Acad Sci. 2000; 899: 44-60.
100. *Wertz K., Siler V., Goraloczyk R.*: Lycopene: modes of action to promote prostate health. Arch. Biochem. Biophys. 2004; 430: 127-34.
101. *Williams A.A., Selvaraj J., Srinivasan C., Sathish S., Rajesh P., Balaji V., Arunakaran J., Balasubramanian K.:* Protective role of lycopene against Aroclor 1254-induced changes on GLUT4 in the skeletal muscles of adult male rat. Drug Chem Toxicol. 2013; 36(3): 320-8.
102. *Wink D.A., Hanbauer I., Grisham M.B., Laval F., Nims R.W., Laval J., Cook J., Pacelli R., Liebmann J., Krishna M., Ford P.C., Mitchell J.B.*: Chemical biology of nitric oxide: regulation and protective and toxic mechanisms. Curr Top Cell Regul. 1996; 34: 159–187.
103. *Yapaing Z., Suping Q.,Weni Y., Zheng X., Hong S., Side Y., Dapu W.*: Antioxidant activity of lycopene extracted from paste towards trichloromethyl peroxyl radical CCl3O2. Food Chem. 2002; 77: 209-12.
104. *Yilmaz S., Atessahin A., Sahna E., Karahan I., Ozer S.:* Protective effect of lycopene on adriamycin-induced cardiotoxicity and nephrotoxicity. Toxicology. 2006; 218: 164-71.
105. *Yonar M.*E.: Protective effect of lycopene on oxidative stress and antioxidant status in *Cyprinus carpio* during cypermethrin exposure. Environ Toxicol. 2013; 28(11): 609-16.
106. *Zechmeister L., LeRosen A.L., Went F.W., Pauling L.*: Prolycopene, a naturally occurring stereoisomer of lycopene. Proc Natl Acad Sci U S A. 1941; 21: 468-74.
107. *Zhang L.X., Cooney R.V., Bertram J.S.*: Carotenoids enhance gap junctional communication and inhibit lipid peroxidation in C3H/10T1/2 cells: relationship to their cancer chemopreventive action. Carcinogenesis. 1991; 12: 2109-14.
108. *Zhang L.X., Cooney R.V., Bertram J.S.*: Carotenoids up-regulate connexin43 gene expression independent of their provitamin A or antioxidant properties. Cancer Res. 1992; 52: 5707-12.

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