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Letter to the editor:

RECENT INSIGHTS INTO THE BIOLOGICAL AND PHARMACOLOGICAL ACTIVITY OF LYCOPENE

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Lycopene is a C40 tetraterpene that is composed of eight isoprene units joined by regular head to tail bindings, except in the middle of the molecule, where tail to tail binding forms an asymmetric structure (Arballo et al., 2021). It is a naturally occurring lipophilic red-colored carotenoid pigment found in many red-colored fruits and vegetables, especially tomatoes (Story et al., 2010; Grabowska et al., 2019; Arballo et al., 2021; Sathasivam et al., 2021). Lycopene cannot be synthesized in the human body and must be obtained from dietary foods (Woodside et al., 2015; Imran et al., 2020). This dietary lycopene is stored in adrenals, liver, and the prostate and in lower concentrations in other parts of the body, such as the brain and skin (Moran et al., 2013; Imran et al., 2020).

Lycopene has a potent antioxidant activity and is important for scavenging reactive oxygen species (ROS) (Imran et al., 2020). Its ability to remove atomic oxygen is ten and two times higher than that of α-tocopherol and β-carotene, respectively (Przybylska, 2020). Because of its numerous health benefits, the interest in lycopene consumption has increased. Additionally, lycopene is beneficial for the prevention and treatment of various diseases, including neurodegenerative diseases like Parkinson's and Alzheimer's (Cho et al., 2018; Joshi et al., 2020; Przybylska, 2020). Administration of high doses of lycopene and its products can cure chronic conditions like cardiovascular diseases, cancer (lung and prostate cancers), non-alcoholic fatty liver disease, neurological disorders, oxidative stress, inflammatory pathways, and male infertility (Shen et al., 2007; Chung et al., 2012; Ip et al., 2015; Abar et al., 2016). In addition, lycopene not only inhibits the proliferation of neoplastic cells but also stimulates their apoptosis and inhibits metastasis (Przybylska, 2020). However, the mechanism by which lycopene executes its bioactivity remains unknown (Arballo et al., 2021). Herein, we compiled the most recent findings regarding the biological and pharmacological activities of lycopene (Table 1).

Table 1: Recent studies on the biological and pharmacological activities of lycopene

Key findings	Reference
Lycopene intake at a dose of 10 mg/kg protects the sperm from oxidative stress and DNA damage by increasing the antioxidant activity and reducing ROS in the varicocele group.	Babaei et al., 2021
Lycopene supplementation showed therapeutic results in antioxidant profile, inflammatory and pathological changes, and collagen deposition in the extracellular hepatic tissue in mice exposed to long-term cigarette smoke. This indicates that lycopene administration may be a potential pharmacological tool for preventing liver damage caused by long-term cigarette smoke exposure.	Rocha et al., 2021
Lycopene dietary supplementation may improve intestinal health by improving intestinal morphology, increasing the tight junction function, preventing inflammatory response, and increasing the antioxidant activity in finishing pigs.	Liu et al., 2021a
Lycopene supplementation alleviated aflatoxin B1-induced intestinal immune and barrier function and increased the antioxidant status in broilers.	Sarker et al., 2021
Lycopene increased the dityrosine-mediated myocardial energy homeostasis disorder by stimulating the respiratory chain complexes I and IV activity and reducing cardiac fatty acid accumulation and myocardial hypertrophy.	Wang et al., 2022
Lycopene may inhibit the increase of creatine kinase-MB following percutaneous coronary intervention (PCI). This proves that lycopene has the ability to prevent post-PCI cardiovascular events. However, further studies are needed to prove this effect.	Asgary et al., 2021
Lycopene prevented di(2-ethylhexyl)phthalate (DEHP) induced mitochondria-associated endoplasmic reticulum (ER) membrane disorder and hepatic mitochondrial dynamics. This study provides novel evidence that mitochondria-ER coupling is a target for lycopene to inhibit DEHP-induced hepatotoxicity.	Zhao et al., 2021b
Lycopene prevented oxidative injury of the intestinal epithelium by altering the Kelch-like ECH-associated protein 1 (Keap1)/nuclear factor erythroid-2 related factor 2 (Nrf2) signaling pathway under deoxynivalenol (DON) exposure. These findings are helpful for future research into the therapeutic uses of lycopene to prevent the harmful effects of DON in humans and/or animals.	Rajput et al., 2021
Lycopene-loaded microemulsion diminished the cognitive impairment in amyloid β-induced Alzheimer's-affected rats by stimulating neurogenesis in the subventricular and hippocampal region by triggering the Wnt/β-catenin pathway.	Ning et al., 2021
Lycopene alleviated the zearalenone-induced oxidative stress in Sertoli cells (SCs) by enhancing the Nrf2 pathway and decreasing apoptosis and autophagy in piglet SCs.	Cao et al., 2021
Lycopene was helpful in allergic rhinitis treatment and was especially effective at high concentrations.	Polat et al., 2021
Lycopene supplementation during the maturation of bovine cumulus-oocyte complexes led to increased quality and rate of blastocyst growth under standard maturation conditions.	Residiwati et al., 2021
Lycopene improved palmitic acid-induced neuroinflammation, possibly by reducing oxidative stress and downregulating toll-like receptor 4 (TLR4)/nuclear factor-kappa B (NF-κB)-p65 axis.	Ugbaja et al., 2021
Lycopene can increase the memory and learning capability of vascular dementia (VaD) gerbils, which may be related to decreased apoptosis and oxidative stress in VaD affected hippocampal neurons.	Chen et al., 2021

Key findings	Reference
Lycopene treatment is a safe and efficient therapeutic method for resistant oral lichen planus, evidenced by decreased level of lipid peroxidation biomarker (8-isoprostane) on treatment with lycopene.	Eita et al., 2021
Lycopene dietary supplementation effectively reversed the high-fat diet (HFD) induced fibrotic, inflammatory, and oxidative stresses. Lycopene showed a potential therapeutic ability to control obesity and related pathologies.	Albrahim and Alonazi, 2021
Lycopene caused a dose-dependent decrease in the anthropometrical and nutritional parameters. Moreover, lycopene induced a significant decrease ($p < 0.05$) of 16–54 % in adipose lipid levels. Lycopene was effective in managing obesity and other anthropometric measurements in obese female rats.	Ugwor et al., 2021
High dosage administration of lycopene in patients with type II diabetes mellitus (T2DM) showed high peripheral antioxidant activity and glycemic control. Consequentially, lycopene may reduce the oxidative stress and manage the pathophysiology of patients with T2DM.	Leh et al., 2021
Lycopene protects from oxygen-glucose deprivation (OGD)-induced autophagic death by inhibiting oxidative stress-dependent activation of AMP-activated protein kinase in SH-SY5Y cells.	Li et al., 2021
Lycopene administration controlled intestinal damage by limiting the loss of intestinal immunoglobulin A and reducing bacterial translocation preceding the ischemia-reperfusion injury.	İkiz et al., 2021
Lycopene supplemented corn enhanced the level of immunoglobulin G in sheep's blood, which improved the transfer of passive immunity to newborn lambs.	Fallah et al., 2021
Lycopene inhibited house dust mite-induced cytokine expression, possibly by suppressing TLR4 activation and decreasing mitochondrial and cytoplasmic ROS levels in respiratory epithelial cells.	Choi et al., 2021
Lycopene reduced hypoxia-induced testicular injury by decreasing prokineticin receptor 2 expression and interleukin 1β and 2. This result shows that lycopene is one of the promising treatments for varicocele testicular injury.	Wang et al., 2021
Lycopene showed potency for treating nephrotoxicity by reducing the oxidative damage caused in the kidney by rifampicin and isoniazid administration.	Bedir et al., 2021
Lycopene administration showed better anti-lipidemic and anti-antioxidant effects in HFD-fed animals as compared to the effects of moringa administration. Lycopene showed higher improvement in male fertility parameters than moringa, possibly by diminishing the oxidative stress.	Greish et al., 2021
Lycopene intake with HFD caused the significantly ($p < 0.05$) high expression of leptin gene and protein in the placenta. Lycopene improved fetal development indicators like average weight and litter weight when compared to the HFD without lycopene.	Sun et al., 2021
Lycopene stimulated nuclear factor erythroid 2-related factor 2 (Nrf2)/heme oxygenase 1 pathway and suppressed the NOD-like receptor family pyrin domain-containing 3 protein inflammasome by increasing the Kupffer cell autophagy, which reduced hepatic ischemia-reperfusion (IR) injury.	Xue et al., 2021
Lycopene treatment may improve DEHP intake caused disturbance in the CYP450 system and hepatotoxicity, including oxidative stress damage, by crosstalk between aryl hydrocarbon receptor-Nrf2 pathway.	Zhao et al., 2021a

Key findings	Reference
Oral lycopene intake protected against acrylamide-induced neurotoxicity in rat brain tissue structure by altering oxidant and antioxidant activities.	Farouk et al., 2021
Lycopene prevented ethanol and palmitoleic acid (EtOH/POA)-induced mitochondrial dysfunction, expression of IL-6, and activation of zymogen by repressing NADPH oxidase activity in rat pancreatic acinar cells.	Lee et al., 2021
Cigarette smoking can elevate nonalcoholic steatohepatitis (NASH) and liver fibrosis in ferrets, which is linked to the downregulation of a key lycopene cleavage enzyme [beta-carotene 9',10'-oxygenase (BCO2)], and damaged antioxidant system in the liver. Consumption of lycopene may inhibit cigarette smoking-stimulated NASH by countering the suppression of BCO2 and weakening the antioxidant enzymatic network.	Mustra Rakic et al., 2021
Lycopene treatment during *in vitro* culture improved embryo development by controlling mitochondria-dependent apoptosis and oxidative damage in pigs.	Kang et al., 2021
Lycopene controlled the growth of oral squamous cell carcinoma (OSCC) by hindering the insulin-like growth factor 1 pathway, demonstrating its potency for OSCC treatment.	Tao et al., 2021
Lycopene consumption significantly reduced seizures and memory loss in rats, possibly through its anticonvulsive effects linked with the nitric oxide pathway. Lycopene administration may be useful for the treatment of patients with epilepsy.	Taskiran and Tastemur, 2021
Lycopene disturbed the metabolic enzymatic activities in muscle fibers, stimulated slow-twitch fibers expression, and improved the respiratory capacity of mitochondria. It was concluded that lycopene disturbed the muscle fibers undergoing aerobic respiration, which indicates that lycopene has a potential beneficial effect on the metabolism of skeletal muscles.	Liu et al., 2021b
Lycopene showed protective effect against estrogen-induced cholestatic liver injury through its anti-inflammatory and antioxidant properties. Hence, lycopene may be considered as one of the potential and efficient drugs against cholestasis during pregnancy, as an oral antifertility substance, and for postmenopausal alternative therapy.	Wadie et al., 2021
Lycopene decreased the severity of mucositis. Hence, it can be used as a potential and effective nutritional substance to counteract radiotherapy problems, particularly in the treatment of cancers located in the head and neck.	Motallebnejad et al., 2020
Lycopene may reduce the hypoxic-ischemic brain damage *in vivo* and OGD-induced *in vitro* primary cortical neurons apoptosis through the Nrf2/NF-κB signaling pathway.	Fu et al., 2020
Lycopene is one of the potent natural antioxidants that reduces and inhibits acute kidney injury by lipid peroxidation and oxidative stress modulation. In addition, lycopene may be effective against nephrotoxicity caused by diclofenac, a nephrotoxic agent.	Rasheed et al., 2020
Lycopene defends neuroblastoma cells from ER stress and oxidative stress-induced damage by inhibiting the protein kinase-like ER kinase/C/EBP-homologous protein signaling pathway, which indicates that it is a promising therapeutic agent for the treatment of neurodegenerative diseases.	Ou et al., 2020
Lycopene attenuates oxidative stress, mitochondrial dysfunction, and apoptosis caused in the hippocampal region by preventing the ROS/c-JUN N-terminal Kinase (JNK) signaling pathway, thereby improving chronic restraint stress-induced hippocampal damage and learning and memory loss.	Zhang et al., 2020

Key findings	Reference
Lycopene decreased cell death in certain cells by modulating the 5'AMP-activated protein kinase-dependent activation of autophagy. Lycopene may improve pancreatitis by inhibiting oxidative stress-induced autophagy impairment or by direct autophagy activation in pancreatic acinar cells.	Choi and Kim, 2020
Lycopene intake reduced ovarian ischemia/reperfusion (IR) injury by proportionately increasing the antioxidant activity. Treatment with lycopene may be beneficial for patients post the detorsion procedure to prevent the IR induced damage.	Yilmaz et al., 2020
Lycopene administration can reduce the harmful effects of irradiation on gametes and germ cells, that can protect the non-treated tissues in patients undergoing cancer radiotherapy.	Dobrzyńska and Gajowik, 2020
Lycopene administration at low doses may reduce the oxidative stress caused by smoke inhalation and stimulate genomic stability. These findings will enhance the understanding of the potential molecular mechanisms of lycopene action against lung cancer.	Cheng et al., 2020
Lycopene treatment showed long-term improvement in the symptoms of oral submucous fibrosis (OSMF).	Arakeri et al., 2020
Lycopene showed anti-cancer effects on oral cancer (OC) development. The result of *in vitro* and *in vivo* studies showed that lycopene may suppress the epithelial-mesenchymal transition process and stimulate apoptosis in OC cells. These findings are helpful for the potential clinical use of lycopene in OC treatment.	Wang et al., 2020
Lycopene had a protective role against DEHP-induced mitophagy in spermatogenic cells in the male mouse. This result provides a new strategy for counteracting the DEHP-induced toxicity by the quality control of mitochondria as a target for lycopene treatment.	Zhao et al., 2020
Lycopene showed potency against embryonic anomalies and yolk sac vasculogenic and placenta-forming defects caused by nicotine by altering the apoptotic, inflammatory, vasculogenic, and oxidative activities.	Park et al., 2020
Lycopene can help to improve oxaliplatin-induced central and peripheral nerve damages by exhibiting anti-apoptotic, anti-inflammatory, and antioxidant properties in the sciatic tissue and brain.	Celik et al., 2020
Lycopene showed neuroprotective effects in the hippocampi of rats against bisphenol A intoxication through its antioxidant activity, mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) pathway activation, and neuronal apoptosis inhibition which enhances learning and memory.	El Morsy and Ahmed, 2020
Lycopene reduced obesity and increased glucose and lipid metabolism by the upregulation of peroxisome proliferator-activated receptor γ, which suggests its novel potential use against obesity and obesity-related disorders.	Zhu et al., 2020
Methotrexate (MTX) is an antineoplastic agent that increases the level of ROS and decreases the level of antioxidants. Lycopene pretreatment improves MTX-stimulated ovarian injury and infertility by its antioxidative properties in rats.	Turkler et al., 2020
Lycopene acts against the effects of bisphenol A on metabolism by its potential antioxidant activity and decreases the expression of tumor necrosis factor-α (TNF-α) in adipose tissue.	Elgawish et al., 2020

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Key findings	Reference
Lycopene inhibited and reversed fibrosis and lipotoxicity-induced inflammation in NASH mice by decreasing the oxidative stress, promising to be a novel compound for the treatment of NASH.	Ni et al., 2020
Lycopene dietary intake decreased water loss during thawing and was efficient in reducing oxidative stress in liver and longissimus lumborum muscles up to 72 h of storage, optimally at 50 mg/kg body weight dosage of lycopene.	Fachinello et al., 2020
Lycopene-rich tomato variety increased glucose tolerance in healthy rats by raising the plasma leptin level that improved insulin sensitivity, but there was no influence on lipid metabolism or carotenoid accumulation.	Hashimoto et al., 2020
Lycopene has anti-anemic activity and enhances immunity in diabetic rats. The results showed low platelet counts, neutrophil-lymphocyte ratio and stable albumin, reduction in neutrophil counts, and low globulin content. Lycopene may be beneficial in balancing basic hematophysiological variables.	Eze et al., 2019
Lycopene provoked apoptosis by decreasing ROS levels and suppressing the β-catenin-c-myc/cyclin D1 axis. Lycopene stimulated apoptosis in gastric cancer cells by disturbing the nuclear translocation of β-catenin and expression of key cell survival genes.	Kim et al., 2019
Lycopene considerably decreased ROS production and pyrene-induced cytotoxicity. In addition, lycopene increased detoxification and antioxidant enzymes, possibly by its elytroid 2-related factor 2-dependent pathways and regulatory effects on aryl hydrocarbon receptors.	Ma et al., 2019
Lycopene eased M2-dominant polarization in adipose tissue macrophages, thereby reducing HFD-stimulated insulin resistance and inflammation in epididymal white adipose tissues and liver.	Chen et al., 2019
Lycopene had beneficial effects on blood cells and hepatic lipids, increased high-density lipoprotein cholesterol, alleviated TNF-α and malondialdehyde, and enhanced the hepatic antioxidant activity.	Róvero Costa et al., 2019
Lycopene intake as tomato sauce exhibited positive effects on liver and cardiac metabolism. Hence, it can be recommended as a nutritious food supplement for the treatment and prevention of cardiac diseases and nonalcoholic hepatic steatosis.	Jesuz et al., 2019
Lycopene inhibited the proliferation of SKOV3 in ovarian cancer cells and enhanced their apoptosis *in vitro*. Apoptosis was possibly facilitated by up-regulation and down-regulation of Bax and Bcl-2 expression, respectively.	Xu et al., 2019b
Lycopene enhanced apoptosis in prostate cancer cell lines. Additionally, lycopene strongly inhibited cell viability and arrested cell cycle in human prostate cancer cells, indicating its effective role in the growth of prostate cell lines.	Soares et al., 2019
Lycopene may act as a radio mitigator at low doses after irradiation. Conversely, combined effect of higher dosages of lycopene and irradiation may increase the mutagenic effects of radiation.	Dobrzyńska et al., 2019
Lycopene restored the cardioprotective effects of ischemic postconditioning on myocardial ischemia-reperfusion injury in hypercholesterolemic rats by ER stress inhibition and reactivation of the reperfusion injury salvage kinase pathway.	Duan et al., 2019
Lycopene decreased oxidative stress and tert-butyl hydroperoxide-simulated cell apoptosis that leads to the activation of the phosphatidylinositol 3-kinase/protein kinase B pathway. Hence, lycopene is considered as one of the potential agents for counteracting oxidative stress-mediated Alzheimer's disease.	Huang et al., 2019

Key findings	Reference
Lycopene may show a protective effect on oxidative stress damage and anti-cardiomyocyte apoptosis caused by myocardial ischemia, possibly by down-regulating the JNK/ERK signaling pathway activation induced by myocardial damage.	Fan et al., 2019
Lycopene dietary intake may decrease fasting blood glucose to reduce gestational diabetes mellitus. This protective property was moderately improved in pregnant women.	Gao et al., 2019
Lycopene administration downregulates events related to the hepatic stellate cell activation by altering lipid metabolism. This indicates that lycopene could be a novel pharmacological agent for the treatment of fibrotic liver diseases.	de Barros Elias et al., 2019
Lycopene and insulin co-administration had a neuroprotective effect in diabetic rats and improved streptozotocin-induced learning and memory loss and apoptotic cell death caused in the hippocampal regions.	Malekiyan et al., 2019

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Conflict of interest

The authors declare no conflict of interest.

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