Biomedical & Pharmacology Journal Vol. **10**(4), 2113-2120 (2017)

A Systematic Review on Lycopene and Its Beneficial Effects

P. VENKATA NAVEEN KUMAR[1], P. ELANGO*[1], S. ASMATHULLA[2] and S. KAVIMANI[3]

[1]Department of Pharmacology Sri Ramachandra Medical College and Research Institute, Porur Chennai, India.
[2]Department of biochemistry Sri ManakulaVinayagar Medical College & Hospital Pondicherry, India.
[3]Department of Pharmacology Mother Theresa Post Graduate Institute & Research Institute of Health Science Pondicherry, India.
*Corresponding author E-mail: drpelango@yahoo.com

http://dx.doi.org/10.13005/bpj/1335

(Received: November 25, 2017; accepted: December 06, 2017)

ABSTRACT

Oxidative stress is an important risk factor for various diseases. Dietary consumption of carotenoids like lycopene attenuates the oxidative stress in human beings, also widely distributed in fruits, vegetables like tomato, watermelon, and guava. Antioxidant, and a free radical scavenger property by its unique structure, it is believed to be primarily responsible for various biological effects, supported by sound scientific evidence.The Present systematic review outlines the currently available data on lycopene sources, structure, its absorption, and its beneficial role in chronic diseases. It shows protective against alzheimer disease by improving cognitive functions by protecting oxidative damage of mitochondrial enzymes and preventing apoptosis. Systemic inflammation exacerbates more co-morbidities in chronic obstructive pulmonary diseases lycopene attenuates this condition by its antioxidant property. It regulates osteoporosis by decreasing bone turnover and osteoclast activity with an increase in osteoclast activity. Lycopene reduces neuropathic pain by increasing the expression of connexin (CX43) expression in the dorsal horn of spinal cord which maintains neuropathic pain.

Keywords: Lycopene,cardiovascular diseases,Alzheimer diseases, Chronic obstructive pulmonary diseases.

INTRODUCTION

Lycopene is an effective antioxidant and non-provitamin-A with a singlet oxygen quenching property and ability to trap peroxyl radicals among various carotenoids[1].It has protects biomolecules from oxidative damage Constrain cell proliferation and modulates communication between cell to cell[2].Naturally,lycopene primarily exists in all-*trans* a,geometric form and most stable. It undergoes *mono or poly* isomerization under the influence of light and heat.Free radical scavenger property of lycopene is ten times that of ±-tocopherol [3].100 times efficient than of Vitamin-E and 125 times of glutathione.It is was registered as a neuroprotective, anti-inflammatory,cognitive enhancer[4] High intake of lycopene and its products were associate with prevention of chronic

Published by Oriental Scientific Publishing Company © 2017

diseases like cancer, cardiovascular diseases and neurological disorders [5]. But the mechanism of its beneficial action is not so clear.Lycopene has postulated in modulating, cellular redox environment possibly by protecting the antioxidant enzyme activity.Anti-neuroinflammatory effect of lycopene is due to inhibition of lipo polysaccharide-induced expression of cyclooxygenase-2 in the nucleus microglia[6].Lycopene shows a synergistic effect in combination with vitamin-E,glabridin,rosmarinic acid, and attenuates atherosclerosis by preventing oxidation of low-density lipoproteins [7].

Lycopene structure & occurrence, absorption, and bioavailability

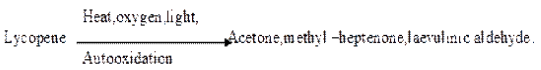
Lycopene is an aliphatic hydrocarbon, with polyunsaturated open straight chain consisting of 2 unconjugated double bonds and 11 conjugated bonds.The biological activity of lycopene is due to the presence of double bonds in its structure, and it lacks terminal ²-ionic ring unlike other carotenoids .Lycopene undergoes photo-oxidation and degradation in the presence of light, and there is a decrease in bioavailability which can be overcome by its incorporation into the oil phase within oil-in-water nanoemulsions[9].All-*trans* form of lycopene is the geometrical isomeric form in fresh tomatoes. *Cis* form of lycopene is thermally unstable, while transform is more stable.*5-Cis* which constitute 4 to 27% and potent antioxidant followed by *9-cis,7-cis,13-cis,11-cis.Cis*-form of lycopene constituents about 50% of total lycopene in human serum and tissues and accumulates in the testis, adrenal gland, and in the liver [10].

Absorption

Most of the carotenoids absorbed in the duodenal.In human serum,lycopene absorption influenced by lipids and lipid-soluble compounds and presence of carotenoids, vitamins, fibers, cooking temperature. Dietary fat meals, Bile acids and micelles favors absorption from a small intestine by a passive transport mechanism, and released into the lymphatic system, to transport into the liver and blood. It gets distributed into LDL low-density lipoprotein and VLDL very low-density lipoprotein fractions. It is soluble in chloroform, benzene, and oil and insoluble in water, ethanol [11]. *Cis*-form of lycopene is the most thermally stable form, with better absorption in humans.It shows distinct property of the all-*trans* form, with a decreased color intensity and more polar nature,solubilized in lipophilic solutions with less prone to crystallization[12]. Lycopene is highly hydrophilic nature and quickly dissolves in oils.Nanoemulsion technique protects antioxidant activity and improves bio-accessibility with a droplet size of in between 100-200nm.A size less than 100nm shows lesser bioavailability and antioxidant activity.The crystalline form of lycopene is one major factor influencing its bioavailability. It builds up in hepatocytes, and spleen in a lesser extent and abundantly in the prostate[13].

Autoxidation of lycopene

Lycopene undergoes autoxidation in the presence of heat, oxygen, light and forms acetone, methyl-heptenone,laevulinic aldehyde.It forms a colorless compound glycoxal,which gives hay or grass-like odors[14].



Lycopene as an antioxidant and anti-inflammatory

Lycopene is an antioxidant,is a free radical scavenger and prevents oxidative destruction in both in *vivo* and *in-vitro*.The inflammatory response is a multifaceted biological process with the involvement of pathophysiological process, i.e., synthesis of cytokines and free radical generation Lipid per oxidation, which consequently initiates the process of inflammation and intern induce the production of reactive oxygen species. Lipopolysaccharides(LPS) are membrane-bound surface receptors of macrophages and substantial component of cell walls, mediate acute inflammatory response, and triggers the release of proinflammatory factors and induce oxidative stress.Uveitis is an autoimmune disorder characterized by intraocular inflammation, with the involvement of retina and vitreous[15].Lycopene's anti-inflammatory property is equivalent to that of dexamethasone in suppressing inflammation and oxidative stress management of uveitis[16].

Lycopene in combination with ascorbic acid and ±-tocopherol showed protection against lipid per oxidation by, inhibiting the release of TNF-± and stimulating(IL-10)synthesis [17].Methanol-

induced hepatotoxicity by increasing oxidative stress and apoptosis.Lycopene showed protection against methanol-induced liver toxicity in similar with fomepizole (methanol intoxication).by inhibiting lipid oxidation & caspases-3 activation[18].Rhinovirus is the common cause for exacerbation of asthma and common cold.Which increased oxidative stress and generated free cells demeaning the production of proinflammatory mediators like IL-6, IL-8, TNF-±. Oxidative stress associated with chronic periodontitis, on activation liberates neutrophils and the reactive oxygen species, matter in the eradication of periodontal tissues. Supplementation of antioxidants inflict the production ROS and constrain the tissue destruction [19].

Lycopene's neuroprotective activity against alzheimer diseases (AD)

Alzheimer's disease is a neurodegenerative disease,with impaired cognitive functions, deposition of amyloid plaques and formation of neuroûbrilary tangles.Oxidative stress, mitochondrial dysfunction, and activation of caspases, ultimately apoptosis, are the factors which are involved in the progress of disease[20].Brain-derived neurotrophic factor (BDNF) is a key protein in the brain neuroplasticity.There is a decline in these levels in hippocampus and cortical region during oxidative stress and apoptosis[21]. Antioxidant complement obstructs the advancement of alzheimer disease ²-amyloid and pro-oxidants promote oxidative stress and initiate apoptosis,

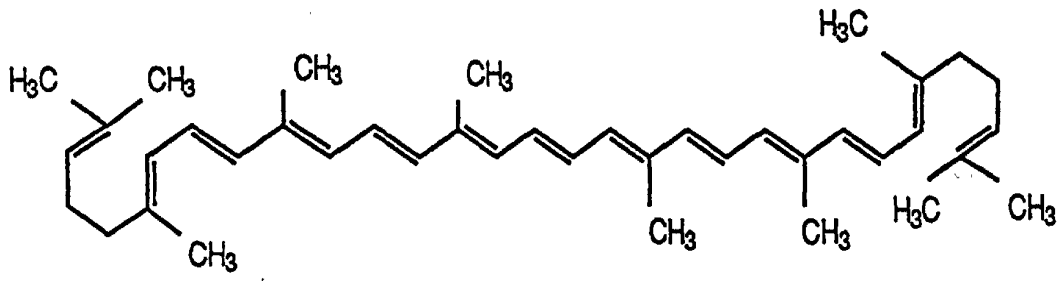


Fig. 1: Structure of lycopene molecular formula and molecular weight 536.9

Table 1: Summary of various lycopene doses and diseases condition in animal models

Diseases conditions	Lycopene dose	Duration of treatment	Route	Strain	References
1.Cognitive-enhancers in Alzheimer disease	2.5-5 mg/kg	3weeks	P.O	Wistar rat	[23]
2.Osteoporosis	15- 45mg/kg	12 weeks	P.O	Female Wistar rats	[33]
3.Anticoagulants & anti-inflammatory	0.1,0.5,1.2g/kg	4 days	P.O	Kingmingstrain mice	[40]
4.Tardive dyskinesia	5mg,10mg/kg	21 days	P.O	Wistar rat	[36]

Table 2: Biological actions of lycopene in diseases

No	Biological properties	Beneficial in diseases condition
1	Antioxidant	Alzheimer disease.
2	Antioxidant & Anti-inflammatory	Cardiovascular disease,uveitis.
3	Systemic anti-inflammatory	Chronic obstructive pulmonary diseases.
4	Gap junction communication	Prostate cancer, neuropathic pain.
5	Anti- Osteoporosis	Regulating osteoclast and osteoblast activity
6	Chronic obstructive pulmonary diseases	Regulating oxidative stress and proinflammatory stress.

neuroinflammation, neurodegeneration,and a decrease in the BDNF[22].

Chronic treatment with lycopene significantly improves the cognitive functions and inhibit apoptosis, by preventing mitochondrial oxidative damage, and a decrease in inflammatory markers and protective properties against ²-amyloid convinced neurotoxicity in rat cortical neurons[23]. Pretreated lycopene remediated ²-amyloid(1-42) induced deficits in learning and memory and mitochondrial dysfunction along with a rise of proinflammatory cytokines and caspase-3 activity in the rat brain significantly reduced in a dose-dependent manner [20].High intake of lycopene with carotenoids(lutein+zeaxanthin)-rich food may be related to reducing the oxidative stress and lowering the risk of alzheimer diseases mortality [21]. Lycopene overcomes insulin resistance induced by long-term intake of fructose, by significantly improving insulin signaling, by up-regulating cholinergic system and improving cognitive functions[22]

Lycopene's cardioprotective activity in cardiovascular disease

Under oxidative stress, there is a generation of reactive oxygen species limited for various cardiovascular disorders .During extreme oxidative stress, body's normal physiological system abort. Supplementation of antioxidants could scavenge the formation of free radicals, by showing therapeutic benefits in cardiovascular diseases .A strong inverse association in between lycopene intake and a decrease in the incidence of cardiovascular diseases[24].Disruption in the functioning of the cardiovascular system leading to the activation of body's immune system and various inflammatory processes results in the production of reactive oxygen species[25].Many contrary reports that show that lycopene administration affects the progression of CVD and its outcomes.Lycopene and lutein are the most important carotenoids found abundantly in fruits and vegetables their combination significantly inhibit oxidative modification of low density lipoprotein in vascular endothelium carotid artery intima–media thickness (CAIMT).Lycopene reduces, cholesterol synthesis, lipid per oxidation and oxidation of low-density lipoprotein (LDL) with up regulation of high-density lipoprotein(HDL)In subjects consuming tomatoes and its products a decrease in carotid artery intima-media thickness and reduction in plasma oxidative damage is observed, Nevertheless,lycopene effect on the progression of cardiovascular diseases remained an uncertain subject in modern medical science and needed further well-designed clinical studies.

Lycopene as a cancer-protective agent

Chronic inflammation is to be suspected in all stages of cancer, in an actively inflamed tissue, causing genomic instability which leads to initiation of cancer. Inflammation can lead to carcinogenesis,by causing changes in gene expression to reinforce proliferation, initiated cells, and combat to apoptosis.Inflammation activates proinflammatory mediators,particularly cytokines,inducing in balance of proangiogenic and anti-angiogenic molecules that leads to tumor neovascularization, which assigns to malignant cell transformation.Abnormal upstream expression of mitogen-activated protein kinase (MAPK)facilitates tumor promotion and progression[26] .

Multiple constricting reports support lycopene anticancer activity in both in vitro & in vivo. It inhibits proliferation of many tumor cells.Lycopene anticarcinogenic property has been postulated predominantly due to its antioxidant function. The increase in serum lycopene in associated with the reduction in prostate-specific antigen(PSA)and a decrease in tumor size shown with daily lycopene supplementation [26].Lipid oxidation and oxidative stress and elevated PSA levels noted in the cancer patient .Recent finding support that,lycopene shown to decrease the prostate growth and PSA antigen in a newly diagnosed patient receiving lycopene daily for about three weeks before induction to radical prostatectomy and reduction in oxidative damage to DNA [27].

Lycopene anti-inflammatory activity in chronic obstructive pulmonary diseases (COPD)

Chronic obstructive pulmonary diseases characterized by inflammation, oxidative stress, hyper secretion of mucus,skeletal muscle debilitated are some of the pathological signs which contribute to loss of lung function. A disproportion in the oxidant-antioxidant system is one of the early events that lead to the initiation of inflammatory reactions in COPD.Cigarette smoke extract(CSE)-induced

matrix metalloproteinase-9expression(MMP) is involved both inflammation and fibrosis.Pre-treated lycopene reduced CSE-mediated MMP-9 induction in a dose-dependent manner by activating reticular activating system (Ras) and enhancing, the protein levels in the cytosolic fraction by inducing extracellular signal-regulated kinases(ERK1/2) and nuclear kappa light chain enhancers of activated B-cells(NF-ºB)activation)[28].Rhinovirus infections are the common cause for exacerbations of asthma and the common cold in adults and children.Oxidative stress and generation of free radicals infect airway epithelial cells causing inflammation to airways and obstruction. Lycopene showed protection against rhinovirus-induced airway inflammation by reducing expression of proinflammatory markers[29]. Systemic inflammation is an important co-morbid condition in COPD.Lycopene in combination therapy with a statin,i.e.,rosuvastatin and omega 3-fatty acids showed a systemic anti-inflammatory effect by significantly lowering serum levels of malondialdehyde, superoxide dismutase [30].

Lycopene protective against osteoporosis

Oxidative stress induces reactive oxygen species, which triggers inflammatory state and adversely affect bone homeostasis and also regulates the activities of osteoclast and osteoblast .Epidemiological studies support that postmenopausal osteoporosis may be due to the production of reactive oxygen species(ROS)[31]The decrease estrogen hormone is associated with bone brittleness and generation of free radicals can adversely affect bone homeostasis [31].By inhibiting osteoclast proliferation and differentiation[32]. Postmenopausal women with reduced levels of vitamins,enzymes,and antioxidants are more prone to osteoporosis .An antioxidant supplementation can counterbalance this effects on bone health. Lycopene pre-treatment of postmenopausal osteoporosis, in which a six-month-old female Wistar rat divided into three groups,one group sham-operated which received vehicle only and ovariectomized group pretreatment with lycopene and other group received bisphosphonates,for about 12weeks.Bone quality assessed, by histomorphometric analysis,lycopene pretreated ovariectomized group had a decrease in bone turnover and osteoclast activity with an increase in both antioxidant enzyme activity and osteoblast activity[33].It also suppressed serum biomarkers of bone metabolism like osteocalcin(s-oc),and serum cross-linked carboxyterminal(S-CTX-1)[34].

Role of lycopene in motor dysfunction and neuropathic Pain

Tardive dyskinesia is an irreversible motor dysfunction characterized by hyperkinetic, abnormal involuntary movements, with orofacial dyskinesia on treatment with an antipsychotic drug in schizophrenia with impaired oxidative stress GABAergic dysfunction[35].Lycopene pretreatment for 21days significantly attenuated impairment in both biochemical, and neuroinflammatory markers, with delayed atypical antipsychotic drug-induced orofacial dyskinesia[36].

Neuropathic pain

Neuropathic pain arises due to the activation of peripheral nociceptors.Toxic chemicals and diseases are often triggering factors for neuropathic pain [37]which are down-regulated, during tissue damage, and oxidative stress. Lycopene on co-administration with gabapentin significantly reversed oxidative stress and hyperalgesia,and cold hyperalgesia induced by partial sciatic nerve ligation (PSNL)[38].

Connexin(CX43)expressed in spinal dorsal horn plays a major role in Gap junctions communications, and maintenance of neuropathic pain.lycopene on repeated intrathecal administration produce a significant up-regulation of CX43 expression in spinal dorsal horn could be a therapeutic approach for the treatment of neuropathic pain[39].

CONCLUSION

High intake of lycopene or high its serum levels are related to reducing the risk of several human diseases like cancers. Generation of free radicals and depletion of free radical scavengers are the primary cause of various diseases.Lycopene being a most potent antioxidant and free radical scavenger exhibits its beneficial effects in various diseases. Lycopene is abundantly present in ***all-trans*** form and gets converted to *cis* form having better bioavailability and concentrated more in

human serum and prostate tissue which decrease the tumor size. Lycopene upon chronic treatment against beta-amyloid improves memory retention and prevents mitochondrial oxidative damage by reducing neuroinflammation by restoring BDNF levels. Lycopene maintains bone homeostasis by regulating activities of osteoclast and osteoblast with an increase in antioxidant enzyme activity. It also involved in the improvement of memory by the acceleration of brain antioxidant defense mechanism by down regulating nitric oxide pathways in neurodegenerative diseases like Alzheimer diseases. Lycopene also regulates drug-induced motor dysfunction by increases GABAergic transmission.

Future aspects

Stress triggers neuroinflammation and inducing nitric oxide and pro-oxidant production with an impairment in neuronal function which all together shapes into a depression. It is a psychiatric disorder with multifactorial neuroinflammatory, neurodegenerative alterations and hypothalamic-pituitary-adrenal HPA axis dysfunctions with a complex etiology. Antidepressants drugs take 2-4 weeks to show clinical improvement in depression. So there is a broad scope for lycopene that could be overwhelmed. However,lycopene, as an antidepressant has not established, is a potent antioxidant,neuroprotective agent,and anti-apoptosis might be a potent molecule for neurodegenerative diseases like depression. Much more quality extensive research work has to done for establishing lycopene as an antidepressant and for stabilizing both pharmacokinetic and pharmacodynamic properties. Large clinical trials are to needed impose the results into humans.

REFERENCES

1. Di Mascio P, Kaiser S, Sies H. Lycopene as the most efficient biological carotenoid singlet oxygen quencher. *Arch Biochem Biophys*; **274**(2):532–8 (1989).
2. Levy J, Bosin E, Feldman B, Giat Y, Miinster A, Danilenko M, et al. Lycopene is a more potent inhibitor of human cancer cell proliferation than either alpha-carotene or beta-carotene. *Nutr Cancer*; **24**(3):257–66 (1995).
3. Böhm F, Edge R, Burke M, Truscott TG. Dietary uptake of lycopene protects human cells from singlet oxygen and nitrogen dioxide - ROS components from cigarette smoke. *J Photochem Photobiol B;* **64**(2–3):176–8 (2001).
4. Sachdeva AK, Chopra K. Lycopene abrogates A^2(1-42)-mediated neuroinflammatory cascade in an experimental model of Alzheimer's disease. *J Nutr Biochem*; **26**(7):736–44 (2015).
5. Frostegård J. Immunity, atherosclerosis and cardiovascular disease. *BMC Med;* **11**:117 (2013).
6. Gärtner C, Stahl W, Sies H. Lycopene is more bioavailable from tomato paste than from fresh tomatoes. *Am J Clin Nutr;* **66**(1):116–22 (1997).
7. Sies H, Stahl W. Lycopene: antioxidant and biological effects and its bioavailability in the human. *Proc Soc Exp Biol Med Soc Exp Biol Med N Y N;* **218**(2):121–4 (1998).
8. Krinsky NI. The antioxidant and biological properties of the carotenoids. *Ann N Y Acad Sci;* **854**:443–7 (1998).
9. Datta M, Taylor ML, Frizzell B. Dietary and Serum Lycopene Levels in Prostate Cancer Patients Undergoing Intensity-Modulated Radiation Therapy. *J Med Food;* **16**(12):1131–7 (2013).
10. Fiedor J, Burda K. Potential Role of Carotenoids as Antioxidants in Human Health and Disease. *Nutrients;* **6**(2):466–88 (2014).
11. Stahl W, Schwarz W, Sundquist AR, Sies H. cis-trans isomers of lycopene and beta-carotene in human serum and tissues. *Arch Biochem Biophys* ; **294**(1):173–7 (1992).
12. Shi J, Le Maguer M, Kakuda Y, Liptay A, Niekamp F. Lycopene degradation and isomerization in tomato dehydration. *Food Res Int;* **32**(1):15–21 (1999).
13. Lee W, Kim TH, Ku S-K, Min K-J, Lee H-S, Kwon TK, et al. Barrier protective effects of withaferin A in HMGB1-induced inflammatory responses in both cellular and animal models. *Toxicol Appl Pharmacol;* **262**(1):91–8 (2012).
14. Shi J, Le Maguer M, Kakuda Y, Liptay A,

Niekamp F. Lycopene degradation and isomerization in tomato dehydration. *Food Res Int;* **32**(1):15–21 (1999).

15. Nussenblatt RB. The natural history of uveitis. *Int Ophthalmol;* **14**(5–6):303–8 (1990).
16. Göncü T, Ouz E, Sezen H, Koçarslan S, Ouz H, Akal A, et al. Anti-inflammatory effect of lycopene on endotoxin-induced uveitis in rats. Arq Bras Oftalmol [Internet] 2016 [cited 2017 Apr 14];79(6). Available from: http://www.gnresearch.org/doi/10.5935/0004-2749.20160102
17. Hazewindus M, Haenen GRMM, Weseler AR, Bast A. The anti-inflammatory effect of lycopene complements the antioxidant action of ascorbic acid and ±-tocopherol. *Food Chem* **132**: 954–8.
18. Kurcer MA, Kurcer Z, Koksal M, Baba F, Ocak AR, Aksoy N, et al. Effect of lycopene on caspase-3 enzyme activation in liver of methanol-intoxicated rats: comparison with fomepizole. *J Med Food;* **13**(4):985–91 (2010).
19. Ambati M, Rani KR, Reddy PV, Suryaprasanna J, Dasari R, Gireddy H. Evaluation of oxidative stress in chronic periodontitis patients following systemic antioxidant supplementation: A clinical and biochemical study. *J Nat Sci Biol Med*; **8**(1):99–103 (2017).
20. Sachdeva AK, Chopra K. Lycopene abrogates A²(1-42)-mediated neuroinflammatory cascade in an experimental model of Alzheimer's disease. *J Nutr Biochem*; **26**(7):736–44 (2015).
21. Min J, Min K. Serum lycopene, lutein and zeaxanthin, and the risk of Alzheimer's disease mortality in older adults. *Dement Geriatr Cogn Disord;* **37**(3–4):246–56 (2014).
22. Yin Q, Ma Y, Hong Y, Hou X, Chen J, Shen C, et al. Lycopene attenuates insulin signaling deficits, oxidative stress, neuroinflammation, and cognitive impairment in fructose-drinking insulin resistant rats. *Neuropharmacology;* **86**:389–96 (2014).
23. Prakash A, Kumar A. Implicating the role of lycopene in restoration of mitochondrial enzymes and BDNF levels in ²-amyloid induced Alzheimerós disease. *Eur J Pharmacol;* **741**:104–11 (2014).
24. Akinloye O, Adaramoye O, Kareem O. Changes in antioxidant status and lipid peroxidation in Nigerian patients with prostate carcinoma. *Pol Arch Med Wewn;* **119**(9):526–32 (2009).
25. Kucuk O, Sarkar FH, Sakr W, Djuric Z, Pollak MN, Khachik F, et al. Phase II randomized clinical trial of lycopene supplementation before radical prostatectomy. *Cancer Epidemiol Biomark Prev Publ Am Assoc Cancer Res Cosponsored Am Soc Prev Oncol;* **10**(8):861–8 (2001).
26. Kundu JK, Surh Y-J. Inflammation: gearing the journey to cancer. *Mutat Res;* **659**(1–2):15–30 (2008).
27. Bowen P, Chen L, Stacewicz-Sapuntzakis M, Duncan C, Sharifi R, Ghosh L, et al. Tomato sauce supplementation and prostate cancer: lycopene accumulation and modulation of biomarkers of carcinogenesis. *Exp Biol Med Maywood NJ;* **227**(10):886–93 (2002).
28. Palozza P, E Simone R, Catalano A, Saraceni F, Celleno L, Cristina Mele M, et al. Modulation of MMP-9 pathway by lycopene in macrophages and fibroblasts exposed to cigarette smoke. *Inflamm Allergy-Drug Targets Former Curr Drug Targets-Inflamm Allergy*; **11**(1):36–47 (2012).
29. Williams EJ, Baines KJ, Smart JM, Gibson PG, Wood LG. Rosuvastatin, lycopene and omega-3 fatty acids: A potential treatment for systemic inflammation in COPD; a pilot study. *J Nutr Intermed Metab;* **5**:86–95 (2016).
30. Verma AK, Aggarwal A, Kumar K. Oxidative stress in chronic obstructive pulmonary disease and effect of lycopene (a dietary supplement) on markers of oxidative stress, inflammation & pulmonary function. *J Evol Med Dent Sci*; **2**(38):7317–7324 (2013).
31. Callaway DA, Jiang JX. Reactive oxygen species and oxidative stress in osteoclastogenesis, skeletal aging and bone diseases. *J Bone Miner Metab;* **33**(4):359–70 (2015).
32. Li M, Zhao L, Liu J, Liu A-L, Zeng W-S, Luo S-Q, et al. Hydrogen peroxide induces G2 cell cycle arrest and inhibits cell proliferation in osteoblasts. Anat Rec Hoboken NJ 2007; **292**(8):1107–13 (2009).
33. Ardawi M-SM, Badawoud MH, Hassan SM, Rouzi AA, Ardawi JMS, AlNosani NM,

et al. Lycopene treatment against loss of bone mass, microarchitecture and strength in relation to regulatory mechanisms in a postmenopausal osteoporosis model. *Bone;* **83**:127–40 (2016).

34. Rao LG, Mackinnon ES, Josse RG, Murray TM, Strauss A, Rao AV. Lycopene consumption decreases oxidative stress and bone resorption markers in postmenopausal women. *Osteoporos Int J Establ Result Coop Eur Found Osteoporos Natl Osteoporos Found USA;* **18**(1):109–15 (2007).
35. Thakur KS, Prakash A, Bisht R, Bansal PK. Beneficial effect of candesartan and lisinopril against haloperidol-induced tardive dyskinesia in rat. *J Renin Angiotensin Aldosterone Syst* ; **16**(4):917–29 (2015).
36. Datta S, Jamwal S, Deshmukh R, Kumar P. Beneficial effects of lycopene against haloperidol induced orofacial dyskinesia in rats: Possible neurotransmitters and neuroinflammation modulation. *Eur J Pharmacol*; **771**:229–35 (2016).
37. Grace PM, Hutchinson MR, Maier SF, Watkins LR. Pathological pain and the neuroimmune interface. *Nat Rev Immunol;* **14**(4):217–31 (2014).
38. Goel R, Tyagi N. Potential Contribution of Antioxidant Mechanism in the Defensive Effect of Lycopene Against Partial Sciatic Nerve Ligation Induced Behavioral, Biochemical and Histopathological Modification in Wistar Rats. *Drug Res*; **66**(12):633–8 (2016).
39. Zhang FF, Morioka N, Kitamura T, Fujii S, Miyauchi K, Nakamura Y, et al. Lycopene ameliorates neuropathic pain by upregulating spinal astrocytic connexin 43 expression. *Life Sci;* **155**:116–22 (2016).
40. Yaping Z, Wenli Y, Weile H, Ying Y. Anti-inflammatory and anticoagulant activities of lycopene in mice. *Nutr Res;* **23**(11):1591–1595 (2003).