

## A New Target in Inflammatory Diseases: Lycopene

Zeynep Karaköy<sup>1</sup> , Elif Cadirci<sup>2</sup> , Busra Dincer<sup>1</sup> 



### ABSTRACT

Inflammation is a response to various injuries, illnesses, and severe trauma. The primary function of inflammation is to combat pathogens, eliminate them from the body, and initiate wound healing. However, inflammation also contributes to numerous diseases, such as cancer, cardiovascular disease, diabetes, obesity, osteoporosis, rheumatoid arthritis, inflammatory bowel disease, and asthma. As the importance of nutrition in maintaining human health has become increasingly recognized, the consumption of natural antioxidants has gained popularity, especially in developed countries. A growing body of research has shown that consuming foods rich in lycopene can protect individuals from a range of conditions, including cancer, heart disease, and other diseases. As a result, lycopene is gaining recognition as a potential protective antioxidant in the fields of medicine and pharmacology. This review aims to highlight the effects of lycopene on inflammatory diseases and provide a foundational understanding for researchers interested in further research on lycopene.

**Keywords:** Lycopene, free radicals, inflammation

### Introduction

Inflammation is the body's primary immune response to harmful stimuli such as allergens and pathogens.<sup>1</sup> In addition to killing pathogens, it initiates tissue repair processes and helps restore homeostasis in damaged areas.<sup>2,3</sup> These stimuli trigger the body's inflammatory processes that begin with the expression of pro-inflammatory cytokines and chemokines. Cytokines activate endothelial cells,<sup>4</sup> leading to increased vascular permeability and facilitating the entry of immune cells into tissues at the site of inflammation.<sup>5</sup>

Furthermore, chemokines attract eosinophils, neutrophils, monocytes, and mast cells to the injury site. Once the infection has been cleared, mechanisms are activated to prevent further damage to the host and begin tissue repair. These control mechanisms increase the expression of anti-inflammatory cytokines to end inflammation and inhibit the expression of pro-inflammatory cytokines. Eventually, the inflammation subsides as inflammatory cells undergo apoptosis, and the tissue returns to homeostasis.<sup>6</sup>

### Inflammatory Mediators

#### Pro-Inflammatory Cytokines

Cytokines are substances in peptide or glycoprotein structure with a weight of 20-30 kD, mainly synthesized from immune cells, including monocytes, macrophages, and lymphocytes.<sup>7</sup> Cytokines are grouped as pro-inflammatory<sup>7</sup> or anti-inflammatory<sup>8</sup>: interleukin (IL)-1, IL-6, IL-12, IL-1 $\beta$ , interferon (IFN)- $\gamma$ , tumor necrosis factor (TNF)- $\alpha$ , and granulocyte-macrophage colony-stimulating factor are proinflammatory cytokines.<sup>5</sup> At the same time, IFN- $\alpha$ , IL-4, IL-10, IL-13, and transforming growth factor- $\beta$  are anti-inflammatory cytokines.<sup>6,9</sup>

Tumor necrosis factor- $\alpha$  is an important pro-inflammatory cytokine of the TNF superfamily, abundantly produced by immune cells during acute inflammation.<sup>3</sup> Tumor necrosis factor- $\alpha$  causes vasodilation and increased vascular permeability, leading to systemic edema.<sup>10</sup>

**Cite this article as:** Karaköy Z, Cadirci E, Dincer B. A new target in inflammatory diseases: Lycopene. *Eurasian J Med.*, 2022;54(Suppl. 1):S23-S28.

<sup>1</sup>Department of Pharmacology, Erzincan Binali Yildirim University, Faculty of Pharmacy, Erzincan, Turkey

<sup>2</sup>Department of Pharmacology, Ataturk University, Faculty of Medicine, Erzurum, Turkey

Received: September 12, 2022

Accepted: October 30, 2022

Publication Date: December 1, 2022

Corresponding author: Busra Dincer  
E-mail: bbasoglu@erzincan.edu.tr



asianjmed.2022.22303

Content of this journal is licensed under a Creative Commons Attribution 4.0 International License.

### Nuclear Factor Kappa-B

Nuclear factor kappa-B (NF- $\kappa$ B) is an inducible transcription factor that regulates the expression of cytokines involved in inflammation.<sup>11</sup> When activated, NF- $\kappa$ B stimulates the transcription of various inflammatory genes. It plays a significant role in the inflammatory response by directly increasing the production of inflammatory cytokines, chemokines, and adhesion molecules; influencing T cell activation, differentiation, and function; and regulating cell proliferation, apoptosis, and morphogenesis<sup>12</sup> (see Figure 1).

### C-Reactive Protein

C-reactive protein (CRP) is an acute-phase protein that is synthesized by the liver. C-reactive protein is found at very low levels in healthy individuals. C-reactive protein levels increase during infections and inflammatory diseases.<sup>13</sup> Its primary function is to coat damaged cells in inflammation, enabling them to be recognized by other immune cells. As such, CRP is a systemic marker of inflammation.<sup>3</sup>

### Reactive Oxygen Species

Stimulating these inflammatory cells by tumor promoters, parasites, bacteria, or particles releases reactive oxygen species (ROS). After reaching the site of inflammation, leukocytes are involved in the process of phagocytosis, which is accompanied by a process called "respiratory burst." That is, they engulf bacteria or foreign particles. At this stage, leukocytes rapidly increase their oxygen uptake. As a result, ROS are produced, such as superoxide anion, lipid peroxyl, hydrogen peroxide, alkoxy, and hydroxyl radicals. Research has shown that the release of ROS increases the expression of intercellular cell adhesion molecules (ICAM), activates NF- $\kappa$ B, and increases inflammation.<sup>14</sup>

### Lycopene

Lycopene, a red carotenoid, was first discovered by Millardet in 1876 as a red pigment in tomatoes, later named "lycopene" by Schunck.<sup>15</sup> It is predominantly found in carrots, watermelon, papaya, gac fruit (red), asparagus, and parsley.<sup>16</sup> Among the various common carotenoids, lycopene has the strongest antioxidant properties.<sup>17</sup> Lycopene is a natural antioxidant and anti-inflammatory agent that can potentially prevent and treat diseases.<sup>18,19</sup>

### Physicochemical Properties of Lycopene

It is a symmetrical tetraterpene composed of 40 carbon and 56 hydrogens (C<sub>40</sub>H<sub>56</sub>) and an isoprene unit (Figure 2). Lycopene is an acyclic isomer of  $\beta$ -carotene,<sup>20</sup> but unlike  $\beta$ -carotene, lycopene lacks the  $\beta$ -ionic ring structure. Therefore, there is no provitamin A activity.

On the other hand, lycopene is a much higher antioxidant than  $\beta$ -carotene and  $\alpha$ -tocopherol (vitamin E).<sup>21</sup>

### Therapeutic Potential of Lycopene

#### Antioxidant Effect

Lycopene is a powerful and important antioxidant. It prevents the oxidation of proteins, lipids, and deoxyribonucleic acid through its action on free radicals.<sup>15,22,23</sup> Free radicals are in excess at the site of inflammation, and these free radicals cause tissue damage. Several studies have found that lycopene can modulate ROS levels.<sup>24</sup> The antioxidant activity of lycopene comes from the conjugated double bond in its structure.<sup>25</sup> Lycopene interacts chemically with ROS and prevents ROS-induced cell damage.<sup>6</sup>

#### Anticancer Effect

Lycopene inhibits the expression of cyclin D1 in G0/G1 phases and arrests the cell cycle.<sup>26</sup> Studies have shown that the level of lycopene in serum and tissues can inhibit the growth of cancer cells in different organs and reduce their carcinogenesis.<sup>16</sup> The anti-inflammatory activity of lycopene is considered a key factor in suppressing the progression of carcinogenesis.<sup>27</sup>

### Possible Side Effect

Lycopenemia is a pigmentation disorder caused by the accumulation of lycopene. The skin color changes to a yellow-orange color. It is caused by the accumulation of lycopene due to excessive consumption of lycopene-rich foods. This accumulation occurs in the stratum corneum with a high lipid content and affinity for lycopene. The symptoms of lycopenemia typically disappear when the dietary intake of lycopene is reduced.<sup>28</sup>

### Lycopene and Inflammation

Lycopene is one of the most studied natural compounds due to its antioxidant, anti-inflammatory, and anticancer properties.<sup>29,30</sup> It positively affects inflammation as it activates the expression of antioxidant genes and regulates the signaling pathways responsible for inducing inflammatory mediators.<sup>15</sup>

### Anti-Inflammatory Effect Mechanism of Lycopene

Lycopene generally exerts its anti-inflammatory activity through the following mechanisms:

- (1) Down-regulation of pro-inflammatory cytokines such as IL-1, IL-6, and TNF- $\alpha$ .

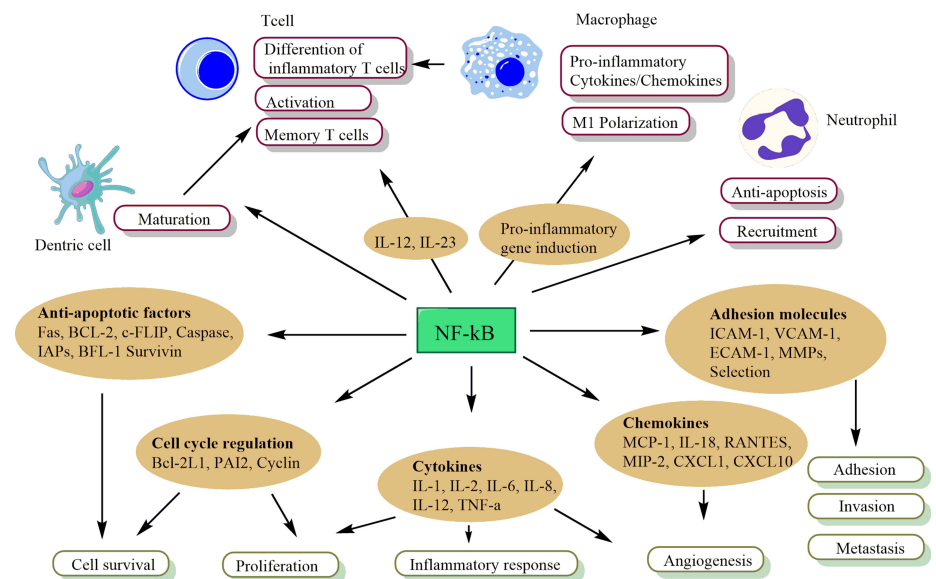


Figure 1. Nuclear factor kappa-B and inflammatory response (Adapted from Ref. 7).

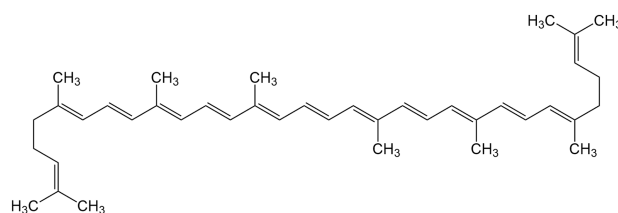


Figure 2. Molecular structure of lycopene.

Lycopene						
Adhesion Molecules ↓ Cytokines ↓	AGE ↓ RAGE ↓	Inflammation-related gene expression ↓	Monocyte endothelial interaction ↓	Leukocyte migration ↓	T lymphocyte activation ↓	COX-2 secretion ↓

**Figure 3.** Anti-inflammatory effects of lycopene (Adapted from Ref. 25). AGE, advanced glycation end products; COX-2, cyclooxygenase 2; RAGE, AGE receptors.

- (2) Reduction of other pro-inflammatory mediators such as inducible nitric oxide synthase (iNOS) and cyclooxygenase 2 (COX-2) expression.
- (3) Reducing the expression of NF-κB.<sup>29</sup>

Inhibiting the extracellular signal-regulated kinase (ERK) and p38 mitogen-activated protein (MAP) kinase in macrophages is another way to reduce inflammation.<sup>29</sup> Figure 3 illustrates the anti-inflammatory effects of lycopene.

Lycopene has an important role in suppressing the inflammatory response. Its effect in this

direction is mainly related to the inhibition of ROS production. In addition, lycopene inhibits the synthesis and expression of pro-inflammatory cytokines, including IL-1, IL-1β, IL-6, and TNF-α.<sup>31</sup> Figure 4 shows the schematic of the anti-inflammatory effect of carotenoids on different inflammatory signaling pathways.

**In-Vivo/In Vitro Lycopene Research**

Long-standing and unresolved inflammation is closely associated with many diseases, including rheumatoid arthritis (RA),<sup>32</sup> inflammatory bowel disease (IBD), atherosclerosis,<sup>33</sup> chronic obstructive pulmonary disease (COPD),<sup>34</sup>

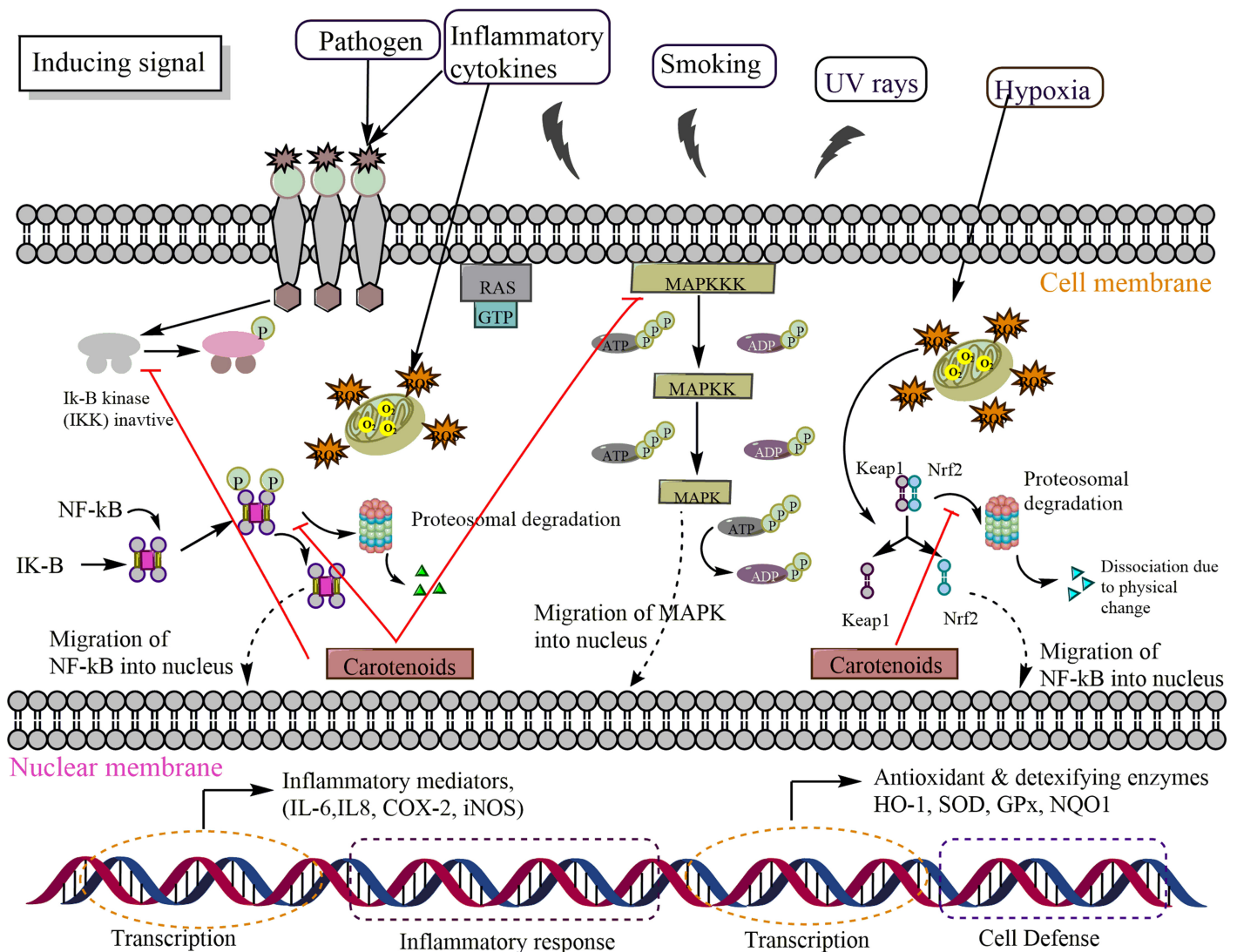
asthma, neurodegenerative diseases, and cancer.<sup>35</sup> Many natural compounds, including lycopene, are used to treat inflammation and inflammatory diseases.<sup>9,36-40</sup> In vivo and in vitro studies with lycopene are summarized in Table 1.

**Lycopene in Inflammatory Diseases**

**Anti-Inflammatory Effect of Lycopene on Asthma and Chronic Obstructive Pulmonary Diseases**

Asthma is a heterogeneous disease caused by inflammation of the airways. It is characterized by airway hypersensitivity to stimuli, airway edema, and increased mucus secretion.<sup>41</sup>

Chronic obstructive pulmonary disease is a progressive, highly mortal, and morbid disease characterized by airway restriction, associated with an abnormal inflammatory response to exposure to risk factors. Inflammation in COPD affects the entire system, not just the airways.<sup>42</sup>



**Figure 4.** Anti-inflammatory effect of carotenoids on different inflammatory signaling pathways (Adapted from Ref. 22).

**Table 1. In Vitro/In Vivo Studies About the Lycopene's Anti-Inflammatory Properties**

In Vitro/In Vivo	Dose	Result	Reference
SW480 human colorectal cancer cells	10, 20, and 30 $\mu$ M Lycopene	↓ COX-2, mRNA expression, and PGE2 production	65
Prostate cancer cells, LNCaP, PC3, and DU145	Lycopene	↓ IL-1, IL-6, IL-8, TNF- $\alpha$ expression	66
Rat pancreatic acinar cell line	5 $\mu$ mol/L Lycopene	ROS, IL-6, NF- $\kappa$ B signaling activation ↓	58
J774A.1 macrophage cell line	0.5, 1.0, and 2.0 $\mu$ M Lycopene	↓ TNF- $\alpha$ , IFN- $\gamma$	44
Airway epithelial cells (Calu-3 cells)	0, 2.5, 5, 10, and 25 $\mu$ g/mL Lycopene	↓ NF- $\kappa$ B inactivation ↓ IL6	67
RAW 264.7 cells	1–10 $\mu$ M Lycopene	↓ IL-6	17
HUVEC	20 $\mu$ M Lycopene	↓ CD14, TLR4, TNF- $\alpha$ , and NF- $\kappa$ B	68
Peripheral blood mononuclear cells (PBMC)	0.25, 0.5, 1.0, 2.0, and 4.0 $\mu$ M Lycopene	↓ TNF- $\alpha$ and IL-1 $\beta$ ; ↑ IL-10, IL-2, and IFN- $\gamma$ ;	69
Male BALB/c mice	4 mg Lycopene in 200 $\mu$ L of water	↓ Eosinophils; ↓ IL-4, IL-5, IL-13	70
Male BALB/c mice	10 mg/kg/day Intra-gastric for 4 weeks	↓ TNF- $\alpha$ , NF- $\kappa$ B, and IL-1 $\beta$	71
L-arginine-induced acute pancreatitis in rats	50 mg/kg Lycopene	↓ TNF- $\alpha$	72
Severe acute pancreatitis from sodium taurocholate in rats	10 mg/kg Lycopene	↓ TNF- $\alpha$ , IL-6 ↓ NF- $\kappa$ B p65	73

COX-2, cyclooxygenase 2; IFN- $\gamma$ , interferon gamma; IL, interleukin; NF- $\kappa$ B, nuclear factor kappa-B; PGE2, prostaglandin E2; ROS, reactive oxygen species; TNF- $\alpha$ , tumor necrosis factor.

The disproportion in the oxidant–antioxidant system is one of the events leading to the onset of inflammatory reactions in COPD. Oxidative stress and the formation of free radicals infect airway epithelial cells, causing inflammation and obstruction in the airways.<sup>42</sup>

Lee et al<sup>43</sup> showed that eosinophils in the lung stimulate T helper type 2 (Th2) cell responses. Therefore, Th2 cells are abundant in the airways, and Th2 cytokines play a very essential role in the pathophysiology of asthma. In addition, matrix metalloproteinase-9 induces the migration of lymphocytes, eosinophils, and neutrophils across basement membranes during tissue injury and repair.

Campos et al<sup>44</sup> showed in both in vitro and in vivo experiments that lycopene inhibits TNF-mediated activation of the NF- $\kappa$ B signaling pathway and reduces the expression of inflammatory cytokines and chemokines.

#### Anti-Inflammatory Effect of Lycopene on Rheumatic Diseases

Rheumatoid arthritis is a common, systemic, and chronic inflammatory disease that causes arthritis in the joints symmetrically. The disease affects about 1% of the world's population, and if left untreated, can lead to joint damage, deformity,

and related disability.<sup>45</sup> Disruption of antioxidant systems in RA and oxidative stress caused by free radicals have an essential role in the etiology of RA.<sup>46</sup> Moia et al<sup>47</sup> reported that nanolycopene might be used as an anti-inflammatory agent to treat RA.

#### Anti-Inflammatory Effect of Lycopene on Cardiovascular Diseases

Inflammation is associated with atherosclerosis, arterial stiffness, and major cardiovascular disease.<sup>48</sup> Oxidative stress is recognized as a cardiovascular risk factor.<sup>49,50</sup> Some research has shown that natural compounds with antioxidant and anti-inflammatory effects may be beneficial in preventing and treating cardiovascular diseases.<sup>51</sup>

Studies have also shown that lycopene can inhibit TNF- $\alpha$ -induced NF- $\kappa$ B activation, expression of ICAM-1, and the interaction between endothelial cells and monocytes. In addition, lycopene reduces the secretion of metalloproteinases by macrophages and inhibits the activation of T lymphocytes. Recently, lycopene has been an effective antiglycation agent, which can reduce the synthesis of advanced glycation end products (AGE) and AGE receptors (RAGE) and further contribute to vascular protection.<sup>6,52</sup>

An in vivo study reported the benefits of lycopene in preventing transplant vasculopathy by showing that intimal hyperplasia and smooth muscle cell proliferation and infiltration of inflammatory cells in allograft vessels were reduced by lycopene administration.<sup>53</sup>

Oxysterols, which result from the auto-oxidation of cholesterol, accumulate in the subendothelial artery layer and support the atherosclerotic process by playing an oxidative and pro-inflammatory role. Lycopene reduces atherosclerotic plaque formation by disrupting oxysterol-induced pro-inflammatory cytokine production and ROS production in macrophages.<sup>52,54</sup>

Considering the aforementioned anti-inflammatory mechanisms (reduction of AGE and RAGE synthesis, inhibition of proinflammatory cytokines and genes involved in inflammation, reduction of adhesion molecules, and downregulation of COX-2), lycopene may be helpful in the treatment of vascular inflammatory disorders.<sup>52</sup>

#### Anti-Inflammatory Effect of Lycopene on Pancreatitis

Pancreatitis is a gastrointestinal disease with significant morbidity and mortality despite modern diagnosis and treatment methods. The severity of the disease mainly depends on the inflammatory responses that occur in the early phase of the disease. Many studies have reported that many natural compounds with antioxidant and anti-inflammatory properties protect pancreatitis.<sup>55,56</sup>

In an experimental pancreatitis model, cerulein binds to cholecystokinin (CCK) receptors and temporarily elevates intracellular Ca<sup>2+</sup> levels. Increasing Ca<sup>2+</sup> activates nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, which produces ROS. Reactive oxygen species with increased levels induce the NF- $\kappa$ B signaling pathway and the expression of inflammatory cytokines (IL-1 $\beta$ , IL 6, and TNF- $\alpha$ ). Thanks to its antioxidant properties, lycopene suppresses NF- $\kappa$ B activation and inhibits the inflammatory cytokine IL-6 in pancreatic acinar cells.<sup>57,58</sup>

In a study on rats, lycopene was found to decrease the levels of the inflammatory cytokines TNF- $\alpha$  and IL-1 $\beta$ , as well as the enzyme myeloperoxidase, and increase the levels of the antioxidant glutathione.<sup>59</sup>

#### Anti-Inflammatory Effect of Lycopene on Inflammatory Bowel Diseases

Inflammatory bowel disease is a recurrent and chronic immune system disorder of unknown etiology that affects millions of people.<sup>60</sup>

Inflammatory bowel diseases are of 2 types: ulcerative colitis and Crohn's disease. Activation of NF- $\kappa$ B induces the expression of many molecules (such as IL-1 $\beta$ , TNF- $\alpha$ , IL-6, IL-8, ICAM-1) involved in the pathogenesis of IBD.<sup>61</sup>

Corticosteroids and 5-aminosalicylates are used in classical treatment. Immunosuppressive and biological agents are used in patients who do not respond to conventional treatment.<sup>36</sup>

However, corticosteroids are not considered an appropriate option in the long term, especially in children, due to their potentially serious side effects, such as osteopenia, growth retardation, and insulin resistance.<sup>62</sup>

Antioxidant and anti-inflammatory natural compounds have been used to treat IBDs.<sup>63</sup> Studies have reported that lycopene alleviates inflammation in colitis. Lycopene treatment aims to reduce symptoms and remission, improve quality of life, and prevent complications.<sup>64</sup>

## Conclusion

Lycopene is an important antioxidant compound in eliminating free radicals released from oxidative stress due to various factors. It not only defends cells from free radical damage but also supports the bonds between cells and develops cell metabolism.

Given its numerous preventive properties that reduce the risk of oxidative stress-related diseases such as atherosclerosis, cardiovascular disease, neurodegenerative disorders, and cancer, it is important for human health and a balanced diet to include foods rich in lycopene.

This review study examined the relationship between lycopene, a bioactive component with different pharmacological benefits such as anti-cancer,<sup>27</sup> antioxidant,<sup>44</sup> cardioprotective,<sup>31</sup> and antihypertensive effects, and the onset and progression of inflammation, as well as the potential role of lycopene in managing these diseases.

There are still many unknowns about the biological function of lycopene, and further research is needed to determine whether the metabolites of lycopene have any biological effects.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept – Z.K., B.D., E.C.; Design – B.D.; Supervision – E.C.; Funding – E.C.; Data Collection and/or Processing – Z.K.; Analysis and/or Interpretation – Z.K., B.D.; Literature Review – Z.K., B.D., E.C.; Writing Manuscript – Z.K., B.D.; Critical Review – Z.K., B.D., E.C.

**Declaration of Interests:** The authors have no conflicts of interest to declare.

**Funding:** The present study was supported by Ataturk University Scientific Research Projects Coordination (grant number TAD-2020-8586).

## References

- Chen L, Deng H, Cui H, et al. Inflammatory responses and inflammation-associated diseases in organs. *Oncotarget*. 2018;9(6):7204-7218. [\[CrossRef\]](#)
- Calder PC, Ahluwalia N, Albers R, et al. A consideration of biomarkers to be used for evaluation of inflammation in human nutritional studies. *Br J Nutr*. 2013;109(suppl 1):S1-S34. [\[CrossRef\]](#)
- Laveti D, Kumar M, Hemalatha R, et al. Anti-inflammatory treatments for chronic diseases: a review. *Inflamm Allergy Drug Targets*. 2013;12(5):349-361. [\[CrossRef\]](#)
- Zhang C. The role of inflammatory cytokines in endothelial dysfunction. *Basic Res Cardiol*. 2008;103(5):398-406. [\[CrossRef\]](#)
- Zhang JM, An J. Cytokines, inflammation, and pain. *Int Anesthesiol Clin*. 2007;45(2):27-37. [\[CrossRef\]](#)
- Palozza P, Parrone N, Catalano A, Simone R. Tomato lycopene and inflammatory cascade: basic interactions and clinical implications. *Curr Med Chem*. 2010;17(23):2547-2563. [\[CrossRef\]](#)
- Arango Duque G, Descoteaux A. Macrophage cytokines: involvement in immunity and infectious diseases. *Front Immunol*. 2014;5:491. [\[CrossRef\]](#)
- Opal SM, DePalo VA. Anti-inflammatory cytokines. *Chest*. 2000;117(4):1162-1172. [\[CrossRef\]](#)
- Polat G, Ugan RA, Cadirci E, Halici Z. Sepsis and septic shock: current treatment strategies and new approaches. *Eurasian J Med*. 2017;49(1):53-58. [\[CrossRef\]](#)
- Reis Machado J, Soave DF, da Silva MV, et al. Neonatal sepsis and inflammatory mediators. *Mediators Inflamm*. 2014;2014:1-10. [\[CrossRef\]](#)
- Lawrence T. The nuclear factor NF- $\kappa$ B pathway in inflammation. *Cold Spring Harb Perspect Biol*. 2009;1(6):a001651-a001651. [\[CrossRef\]](#)
- Liu T, Zhang L, Joo D, Sun SC. NF- $\kappa$ B signaling in inflammation. *Signal Transduct Target Ther*. 2017;2(1):17023. [\[CrossRef\]](#)
- Sproston NR, Ashworth JJ. Role of C-reactive protein at sites of inflammation and infection. *Front Immunol*. 2018;9:754. [\[CrossRef\]](#)
- Huang MT, Ghai G, Ho CT. Inflammatory process and molecular targets for antiinflammatory nutraceuticals. *Compr Rev Food Sci Food Saf*. 2004;3(4):127-139. [\[CrossRef\]](#)
- Caseiro M, Ascenso A, Costa A, Creagh-Flynn J, Johnson M, Simões S. Lycopene in human health. *LWT*. 2020;127:109323. [\[CrossRef\]](#)
- Mirahmadi M, Azimi-Hashemi S, Saburi E, Kamali H, Pishbin M, Hazizadeh F. Potential inhibitory effect of lycopene on prostate cancer. *Biomed Pharmacother*. 2020;129:110459. [\[CrossRef\]](#)
- Feng D, Ling WH, Duan RD. Lycopene suppresses LPS-induced NO and IL-6 production by inhibiting the activation of ERK, p38MAPK, and NF- $\kappa$ B in macrophages. *Inflamm Res*. 2010;59(2):115-121. [\[CrossRef\]](#)
- Gegin S, Celikel S, Celik D, Pazarli AC. Evaluation of interleukin-6, leukotriene B-4, and nitric oxide levels in exhaled breath condensate of asymptomatic obese individuals: are obese patients under risk of developing asthma? *Eurasian J Med*. 2020;52(1):25-28. [\[CrossRef\]](#)
- Celik H, Kucukler S, Ozdemir S, et al. Lycopene protects against central and peripheral neuropathy by inhibiting oxaliplatin-induced ATF-6 pathway, apoptosis, inflammation and oxidative stress in brains and sciatic tissues of rats. *Neurotoxicology*. 2020;80:29-40. [\[CrossRef\]](#)
- Khoo HE, Prasad KN, Kong KW, Jiang Y, Ismail A. Carotenoids and their isomers: color pigments in fruits and vegetables. *Molecules*. 2011;16(2):1710-1738. [\[CrossRef\]](#)
- van Steenwijk HP, Bast A, de Boer A. The role of circulating lycopene in low-grade chronic inflammation: a systematic review of the literature. *Molecules*. 2020;25(19):4378. [\[CrossRef\]](#)
- Magne TM, da Silva de Barros AO, de Almeida Fechine PB, Alencar LMR, Ricci-Junior E, Santos-Oliveira R. Lycopene as a multifunctional platform for the treatment of cancer and inflammation. *Rev Bras Farmacogn*. 2022;32(3):321-330. [\[CrossRef\]](#)
- Buyuklu M, Kandemir FM, Ozkaraca M, et al. Beneficial effects of lycopene against contrast medium-induced oxidative stress, inflammation, autophagy, and apoptosis in rat kidney. *Hum Exp Toxicol*. 2015;34(5):487-496. [\[CrossRef\]](#)
- Bin-Jumah MN, Nadeem MS, Gilani SJ, et al. Lycopene: a natural arsenal in the war against oxidative stress and cardiovascular diseases. *Antioxidants (Basel)*. 2022;11(2):232. [\[CrossRef\]](#)
- Kelkel M, Schumacher M, Dicato M, Diederich M. Antioxidant and anti-proliferative properties of lycopene. *Free Radic Res*. 2011;45(8):925-940. [\[CrossRef\]](#)
- Obermüller-Jevic UC, Olano-Martin E, Corbacho AM, et al. Lycopene inhibits the growth of normal human prostate epithelial cells in vitro. *J Nutr*. 2003;133(11):3356-3360. [\[CrossRef\]](#)
- Ono M, Takeshima M, Nakano S. Mechanism of the anticancer effect of lycopene (tetraterpenoids). *Enzymes*. 2015:139-166. [\[CrossRef\]](#)
- Khan UM, Sevindik M, Zarrabi A, et al. Lycopene: food sources, biological activities, and human health benefits. *Oxid Med Cell Longev*. 2021;2021:2713511. [\[CrossRef\]](#)
- Laranjeira T, Costa A, Faria-Silva C, et al. Sustainable valorization of tomato by-products to obtain bioactive compounds: their potential in inflammation and cancer management. *Molecules*. 2022;27(5):1701. [\[CrossRef\]](#)
- Aydin S, Palabiyik SS, Erkekoglu P, Sahin G, Başaran N, Giray BK. The carotenoid lycopene protects rats against DNA damage induced by ochratoxin A. *Toxicol*. 2013;73:96-103. [\[CrossRef\]](#)

31. Przybylska S, Tokarczyk G. Lycopene in the prevention of cardiovascular diseases. *Int J Mol Sci.* 2022;23(4):1957. [\[CrossRef\]](#)
32. Demoruelle MK, Deane KD, Holers VM. When and where does inflammation begin in rheumatoid arthritis? *Curr Opin Rheumatol.* 2014;26(1):64-71. [\[CrossRef\]](#)
33. Galkina E, Ley K. Immune and inflammatory mechanisms of atherosclerosis (\*). *Annu Rev Immunol.* 2009;27(1):165-197. [\[CrossRef\]](#)
34. Bathoorn E. Airways inflammation and treatment during acute exacerbations of COPD. *Int J Chron Obstruct Pulmon Dis.* 2008;3:217-229. [\[CrossRef\]](#)
35. Zhang X, Liu X, Guo Y, Wu F. Strategies for visualizing inflammation. *View.* 2021;2(1):20200025. [\[CrossRef\]](#)
36. Veauthier B, Hornecker JR. Crohn's disease: diagnosis and management. *Am Fam Phys.* 2018;98(11):661-669.
37. Odabasoglu F, Halici Z, Cakir A, et al. Beneficial effects of vegetable oils (corn, olive and sunflower oils) and  $\alpha$ -tocopherol on anti-inflammatory and gastrointestinal profiles of indomethacin in rats. *Eur J Pharmacol.* 2008;591(1-3):300-306. [\[CrossRef\]](#)
38. Cadirci E, Altunkaynak BZ, Halici Z, et al. Alpha-lipoic acid as a potential target for the treatment of lung injury caused by cecal ligation and puncture-induced sepsis model in rats. *Shock.* 2010;33(5):479-484. [\[CrossRef\]](#)
39. Yıldız MO, Çelik H, Caglayan C, Genç A, Doğan T, Satıcı E. Neuroprotective effects of carvacrol against cadmium-induced neurotoxicity in rats: role of oxidative stress, inflammation and apoptosis. *Metab Brain Dis.* 2022;37(4):1259-1269. [\[CrossRef\]](#)
40. Polat B, Halici Z, Cadirci E, et al. The effect of alpha-lipoic acid in ovariectomy and inflammation-mediated osteoporosis on the skeletal status of rat bone. *Eur J Pharmacol.* 2013;718(1-3):469-474. [\[CrossRef\]](#)
41. Kudo M, Ishigatsubo Y, Aoki I. Pathology of asthma. *Front Microbiol.* 2013;4:263. [\[CrossRef\]](#)
42. 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.* 2013;2(38):7317-7323. [\[CrossRef\]](#)
43. Lee CM, Chang JH, Moon DO, et al. Lycopene suppresses ovalbumin-induced airway inflammation in a murine model of asthma. *Biochem Biophys Res Commun.* 2008;374(2):248-252. [\[CrossRef\]](#)
44. Campos KKD, Araújo GR, Martins TL, et al. The antioxidant and anti-inflammatory properties of lycopene in mice lungs exposed to cigarette smoke. *J Nutr Biochem.* 2017;48:9-20. [\[CrossRef\]](#)
45. Renju GL, Muraleedhara Kurup G, Saritha Kumari CH. Anti-inflammatory activity of lycopene isolated from *Chlorella marina* on type II collagen induced arthritis in Sprague Dawley rats. *Immunopharmacol Immunotoxicol.* 2013;35(2):282-291. [\[CrossRef\]](#)
46. Kalpakcioglu B, Şenel K. The interrelation of glutathione reductase, catalase, glutathione peroxidase, superoxide dismutase, and glucose-6-phosphate in the pathogenesis of rheumatoid arthritis. *Clin Rheumatol.* 2008;27(2):141-145. [\[CrossRef\]](#)
47. Moia VM, Leal Portilho F, Almeida Pádua T, et al. Lycopene used as anti-inflammatory nanodrug for the treatment of rheumatoid arthritis: animal assay, pharmacokinetics, ABC transporter and tissue deposition. *Colloids Surf B Biointerfaces.* 2020;188:110814. [\[CrossRef\]](#)
48. Ünlü Y, Karapolat S, Karaca Y, Kızıltunç A. Comparison of levels of inflammatory markers and hemostatic factors in the patients with and without peripheral arterial disease. *Thromb Res.* 2006;117(4):357-364. [\[CrossRef\]](#)
49. Ari E, Kaya Y, Demir H, et al. Oxidative DNA damage correlates with carotid artery atherosclerosis in hemodialysis patients. *Hemodial Int.* 2011;15(4):453-459. [\[CrossRef\]](#)
50. Aksakal E, Akaras N, Tanboga IH, et al. Relationship between oxidative stress and cardiomyopathic changes in ovariectomized rats. *Cardiology.* 2011;119(4):235-241. [\[CrossRef\]](#)
51. Cinar I, Yayla M, Tavaci T, et al. In vivo and in vitro cardioprotective effect of gossypin against isoproterenol-induced myocardial infarction injury. *Cardiovasc Toxicol.* 2022;22(1):52-62. [\[CrossRef\]](#)
52. Mozos I, Stoian D, Caraba A, Malainer C, Horbańczuk JO, Atanasov AG. Lycopene and vascular health. *Front Pharmacol.* 2018;9:521. [\[CrossRef\]](#)
53. He Y, Xia P, Jin H, Zhang Y, Chen B, Xu Z. Lycopene ameliorates transplant arteriosclerosis in vascular allograft transplantation by regulating the NO/cGMP pathways and rho-associated kinases expression. *Oxid Med Cell Longev.* 2016;2016:3128280. [\[CrossRef\]](#)
54. Palozza P, Simone R, Catalano A, et al. Lycopene prevention of oxysterol-induced proinflammatory cytokine cascade in human macrophages: inhibition of NF- $\kappa$ B nuclear binding and increase in PPAR $\gamma$  expression. *J Nutr Biochem.* 2011;22(3):259-268. [\[CrossRef\]](#)
55. Kılıç Y, Geyikoglu F, Çolak S, Turkez H, Bakır M, Hsseinigouzdagani M. Carvacrol modulates oxidative stress and decreases cell injury in pancreas of rats with acute pancreatitis. *Cytotechnology.* 2016;68(4):1243-1256. [\[CrossRef\]](#)
56. Bakır M, Geyikoglu F, Colak S, Turkez H, Bakır TO, Hosseinigouzdagani M. The carvacrol ameliorates acute pancreatitis-induced liver injury via antioxidant response. *Cytotechnology.* 2016;68(4):1131-1146. [\[CrossRef\]](#)
57. Choi S, Kim H. The remedial potential of lycopene in pancreatitis through regulation of autophagy. *Int J Mol Sci.* 2020;21(16):5775. [\[CrossRef\]](#)
58. Kang M, Park KS, Seo JY, Kim H. Lycopene inhibits IL-6 expression in cerulein-stimulated pancreatic acinar cells. *Genes Nutr.* 2011;6(2):117-123. [\[CrossRef\]](#)
59. Özkan E, Akyüz C, Dulundu E, et al. Protective effects of lycopene on cerulein-induced experimental acute pancreatitis in rats. *J Surg Res.* 2012;176(1):232-238. [\[CrossRef\]](#)
60. M'Koma AE. Inflammatory bowel disease: an expanding global health problem. *Clin Med Insights Gastroenterol.* 2013;6:33-47. [\[CrossRef\]](#)
61. Sartor RB. Mechanisms of Disease: pathogenesis of Crohn's disease and ulcerative colitis. *Nat Clin Pract Gastroenterol Hepatol.* 2006;3(7):390-407. [\[CrossRef\]](#)
62. Amaro F, Chiarelli F. Growth and puberty in children with inflammatory bowel diseases. *Biomedicine.* 2020;8(11):458. [\[CrossRef\]](#)
63. Yong Y, Fang B, Huang Y, et al. Tea tree oil Terpinen-4-ol protects gut barrier integrity by upregulation of tight junction proteins via the ERK1/2-signaling pathway. *Front Nutr.* 2021;8:805612. [\[CrossRef\]](#)
64. Głąbska D, Guzek D, Zakrzewska P, Włodarek D, Lech G. Lycopene, lutein and zeaxanthin may reduce faecal blood, mucus and pus but not abdominal pain in individuals with ulcerative colitis. *Nutrients.* 2016;8(10):613. [\[CrossRef\]](#)
65. Cha JH, Kim WK, Ha AW, Kim MH, Chang MJ. Anti-inflammatory effect of lycopene in SW480 human colorectal cancer cells. *Nutr Res Pract.* 2017;11(2):90-96. [\[CrossRef\]](#)
66. Jiang LN, Liu YB, Li BH. Lycopene exerts anti-inflammatory effect to inhibit prostate cancer progression. *Asian J Androl.* 2018;21(1):80-85. [\[CrossRef\]](#)
67. Saedisomeolia A, Wood LG, Garg ML, Gibson PG, Wark PAB. Lycopene enrichment of cultured airway epithelial cells decreases the inflammation induced by rhinovirus infection and lipopolysaccharide. *J Nutr Biochem.* 2009;20(8):577-585. [\[CrossRef\]](#)
68. Bae JW, Bae JS. Barrier protective effects of lycopene in human endothelial cells. *Inflamm Res.* 2011;60(8):751-758. [\[CrossRef\]](#)
69. Bessler H, Salman H, Bergman M, Alcalay Y, Djaldetti M. In vitro effect of lycopene on cytokine production by human peripheral blood mononuclear cells. *Immunol Investig.* 2008;37(3):183-190. [\[CrossRef\]](#)
70. Hazlewood LC, Wood LG, Hansbro PM, Foster PS. Dietary lycopene supplementation suppresses Th2 responses and lung eosinophilia in a mouse model of allergic asthma. *J Nutr Biochem.* 2011;22(1):95-100. [\[CrossRef\]](#)
71. He Q, Zhou W, Xiong C, Tan G, Chen M. Lycopene attenuates inflammation and apoptosis in post-myocardial infarction remodeling by inhibiting the nuclear factor- $\kappa$ B signaling pathway. *Mol Med Rep.* 2015;11(1):374-378. [\[CrossRef\]](#)
72. El-Ashmawy NE, Khedr NF, El-Bahrawy HA, Hamada OB. Suppression of inducible nitric oxide synthase and tumor necrosis factor-alpha level by lycopene is comparable to methylprednisolone in acute pancreatitis. *Dig Liver Dis.* 2018;50(6):601-607. [\[CrossRef\]](#)
73. Lv JC, Wang G, Pan SH, Bai XW, Sun B. Lycopene protects pancreatic acinar cells against severe acute pancreatitis by abating the oxidative stress through JNK pathway. *Free Radic Res.* 2015;49(2):151-163. [\[CrossRef\]](#)

## Vitamin D in Behcet's Disease, a Brief Review of the Literature

Mehmet Melikoglu<sup>1</sup> , Mestan Sahin<sup>2</sup> , Meltem Alkan Melikoglu<sup>3</sup> 



**Cite this article as:** Melikoglu M, Sahin M, and Alkan Melikoglu M. Vitamin D in behcet's disease, a brief review of the literature. *Eurasian J Med.* 2022;54(Suppl. 1):S29-S33.

<sup>1</sup>Ataturk University School of Medicine, Dermatology, Erzurum, Turkey

<sup>2</sup>Department of Rheumatology, Ataturk University School of Medicine, Internal Medicine, Erzurum, Turkey

<sup>3</sup>Department of Rheumatology, Ataturk University School of Medicine, Physical Medicine and Rehabilitation, Erzurum, Turkey

Received: September 20, 2022

Accepted: November 23, 2022

Publication Date: December 1, 2022

Corresponding author: Meltem Alkan Melikoglu  
E-mail: [mamelikoglu@gmail.com](mailto:mamelikoglu@gmail.com)

DOI 10.5152/eurasianjmed.2022.22300



Content of this journal is licensed under a Creative Commons Attribution 4.0 International License.

### ABSTRACT

Behcet's disease is a chronic vasculitis of unknown etiopathogenesis. Serum vitamin D levels have been reported to be associated with a variety of inflammatory and autoimmune diseases one of which is Behcet's disease. The previous studies about vitamin D in Behcet's disease seem to be focused on 4 main categories; the studies evaluating serum vitamin D levels between patients with Behcet's disease and controls, the studies evaluating serum vitamin D in the susceptibility and pathogenesis of Behcet's disease, the studies evaluating serum vitamin D in clinical involvements and activity of Behcet's disease, and the studies evaluating the effect of serum vitamin D replacement in Behcet's disease.

The aim of this manuscript was to evaluate the results of the studies on serum vitamin D in Behcet's disease and review the literature.

**Keywords:** Behcet's disease, Behcet's syndrome, vitamin D, hydroxy vitamin D

### Introduction

Behcet's disease (BD) is a chronic vasculitis of unknown etiopathogenesis.<sup>1</sup> Since the disease was first described in 1937 by Hulusi Behcet as a characteristic triad including oral and genital aphthous ulcers and relapsing iritis, its clinical spectrum was highly enlarged.<sup>2-4</sup> The disease appears to be frequent in the Mediterranean region, Middle East, and Far East, mostly in Turkey and Japan.<sup>5,6</sup>

The cause and pathogenesis of the disease have not been clarified yet. However, genetic factors seem to be one of the major possible factors that take part in pathogenesis.<sup>1,7,8</sup> Despite some genetic research, the mode of inheritance is not clear. On the basis of genetic factors, the interactions between environmental or other several factors have been suggested as causative factors.<sup>9-11</sup>

The immunological processes and oxidative stress have been investigated as actors in the disease's development and progression.<sup>12-16</sup> Endothelial cell injury may play an important role in the pathogenesis and immunopathology of this systemic vasculitis.<sup>17-20</sup> Some adhesion molecules were also investigated as related factors.<sup>21</sup>

Today BD, with its highly enlarged clinical spectrum, is a multisystemic vasculitis. Vascular involvements are one of the basic characteristics of the disease.<sup>22,23</sup> However, it can affect almost all organs and systems.<sup>3,24-26</sup> In addition to the classical triad, dermatological, musculoskeletal, pulmonary, cardiovascular, gastrointestinal, and nervous system involvements were reported.<sup>27</sup>

Behcet's disease may progress with relapses and remissions.<sup>28</sup> There is no routine test to evaluate the activity of BD.<sup>29</sup> Although some laboratory markers have been suggested to be associated with BD clinical activity, the assessments of a patient with BD are mainly clinical evaluations.<sup>30,31</sup>

As a chronic multisystemic vasculitis, BD may affect the quality of life (QoL) and related factors.<sup>32</sup> It was reported that BD disease activity can affect QoL, and a patient's impression of