Circulating Lycopene in Inflammation

Subjects: Food Science & Technology

Contributor: Hidde P. van Steenwijk , Aalt Bast , Alie de Boer

In recent years, it has become clear that low-grade chronic inflammation is involved in the onset and progression of many non-communicable diseases. Many studies have investigated the association between inflammation and lycopene, however, results have been inconsistent. This review reveals that there is strong evidence indicating that lower circulating lycopene concentrations are related with higher inflammation biomarkers in patients with various diseases. Even though supplementation with lycopene or an increased intake of tomatoes does result in an increase in circulating lycopene, there is little evidence that the lycopene increase also results in relieving this inflammation. This phenomenon, also known as the "antioxidant paradox" limits the added value of lycopene supplementation in both patients and healthy individuals.

carotenoids phytochemicals bioactive nutrition antioxidant paradox

1. Introduction

The understanding of health has changed in recent years: in addition to medicine and pharmacology, there has been an increasing interest in lifestyle medicine in which nutrition plays a pivotal role [1]. In addition to conventional drug therapies, lifestyle adjustments, such as dietary changes, are also advised to reduce disease. Diets with a high proportion of fruits and vegetables seem to have a particularly positive effect on nutritional status as well as different non-communicable diseases, such as heart diseases, neurodegenerative diseases, and diabetes type II. As most non-communicable diseases are partially affected by inflammation, more research is being conducted on potential anti-inflammatory substances derived from fruits and vegetables [2][3][4][5][6].

1.1. Low-Grade Chronic Inflammation

Previous research has shown that the onset and progression of many non-communicable diseases, including heart diseases, neurodegenerative diseases, and diabetes type II, are (partly) related to, or affected by inflammation: low-grade chronic inflammation is central to many different symptoms from which patients suffer in these conditions. Chronic inflammation is believed to aggravate various mechanisms that reflect poor health, including elevated blood pressure, high blood sugar, excessive waist circumference, and abnormal cholesterol or triglyceride levels (the so-called "deadly quartet") [7]. In normal homeostasis, the function of inflammation is to eliminate the initial cause of cell injury, dispose of necrotic cells and damaged tissue caused by both the injury and the inflammation, and to initiate tissue repair. This natural response, acute inflammation, is a critical survival mechanism used by all higher vertebrates [8]. However, if acute inflammation is not resolved, it can lead to chronic inflammation, which is not part of the body's natural healing process and can constitute a damaging process.

Damaged tissues release pro-inflammatory cytokines and other biological inflammatory mediators into the circulation, converting tissue-based low-grade inflammation into a systemic inflammatory condition. Moreover, autoimmune disorders and long-term exposure to irritants can also lead to a systemic inflammatory condition [8][9][10]. The inflammatory response is the coordinated activation of signaling pathways that regulate inflammatory mediator levels in resident tissue cells and inflammatory cells recruited from the blood. Although inflammatory response processes depend on the precise nature of the initial stimulus and its location in the body, for example, bacterial pathogens trigger Toll-like receptors (TLRs) and viral infections trigger type I interferons (IFN), they all share a common mechanism, which can be summarized as follows: (1) Cell surface pattern receptors recognize detrimental stimuli; (2) inflammatory pathways are activated; (3) inflammatory markers are released; and (4) inflammatory cells are recruited [9][11]. Inflammatory stimuli activate intracellular signaling pathways that subsequently activate the production of inflammatory mediators. Primary inflammatory stimuli, including microbial products and cytokines such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α), mediate inflammation through interaction with the TLRs, IL-1 receptor (IL-1R), IL-6 receptor (IL-6R), and the TNF receptor (TNFR). This receptor activation triggers important intracellular signaling pathways, including the mitogen-activated protein kinase (MAPK), nuclear factor kappa-B (NF-κB), NF-E2 p45-related factor 2 (Nrf2), and Janus kinase (JAK)- signal transducer, and activator of transcription (STAT) pathways [11]. In the state of low-grade chronic inflammation, a typical inflammatory stimulator or pathogen can no longer be determined, and inflammatory stimuli and pathways remain activated. Inflammatory stimuli, such as IL-6 and C-reactive protein (CRP), can then be used as biomarkers to measure inflammation [12]. Low grade inflammation is involved in the progression of many non-communicable diseases, but also seems to affect apparently healthy people as a consequence of smoking, stress, or alcohol consumption [8]. A wealth of epidemiological evidence indicates that overall health is strongly influenced by diets with a high proportion of fruits and vegetables [2][3][4][13][14]. Phytochemicals with anti-inflammatory activity present in fruits and vegetables are believed to be largely responsible for overall health. Therefore, new possibilities may exist in the reduction and prevention of non-communicable diseases by increasing the intake of anti-inflammatory food (ingredients) in both healthy and diseased individuals [15][16][17].

1.2. Lycopene

One group of nutritional compounds that has been suggested to elicit anti-inflammatory effects are carotenoids. As carotenoids are pigments in photosynthetic tissue, they are ubiquitous in leafy green vegetables. In non-photosynthetic tissue, carotenoids are responsible for the characteristic coloration of fruits such as red tomatoes, orange carrots, and red flesh in watermelon [18][19]. Of all carotenoids, a substantial amount of research has been conducted on the acyclic lycopene, present in e.g.; tomatoes.

1.2.1. Physicochemical Properties of Lycopene

Lycopene has a chemical formula of C40H56 and like all carotenoids, is a tetraterpene; assembled from eight isoprene units that are solely composed of hydrogen and carbon [20]. Lycopene is an acyclic isomer of β-carotene, however, unlike β-carotene lycopene lacks the β-ionic ring structure. Therefore, it lacks provitamin A activity [20][21]. However, lycopene is one of the most potent antioxidants, with a singlet-oxygen-quenching ability twice as high as

that of β-carotene and ten times higher than that of α-tocopherol (Vitamin E) [22]. Lycopene is a highly unsaturated, open-chain hydrocarbon containing eleven conjugated and two non-conjugated double bonds arranged in a linear array. The double bonds in lycopene can undergo isomerization from trans to cis isomers by thermal energy, chemical reactions, and light [20][21]. The all-trans isomeric form is primarily present in nature, followed by the 5-cis, 9-cis, 13-cis, and 15-cis isomeric forms. Several methods for analysis of circulating lycopene are described. Methods differ in that (i) either plasma or serum lycopene is measured, (ii) multiple isomers, trans-lycopene or total lycopene are measured, (iii) circulating lycopene is adjusted for total cholesterol. The correction for total cholesterol has been made in more recent intervention studies because there is a risk of carotenoid status being misinterpreted in subjects on cholesterol-lowering therapy if they rely on crude serum or plasma levels.

1.2.2. Lycopene Kinetics after Oral Administration: Absorption, Distribution, Metabolism, Excretion

Absorption of lycopene is similar to that of other lipid soluble compounds. Ingested lycopene is incorporated into dietary lipid micelles and absorbed across the gastrointestinal tract via passive diffusion into the intestinal mucosal lining. Then they are incorporated into chylomicrons and released into the lymphatic system for transport to the liver. Lycopene is transported by lipoproteins in the blood for distribution to the different organs [23]. Because of its lipophilic nature, the primary carrier of lycopene is LDL and not HDL [24]. Generally, 10–30% of dietary lycopene is absorbed with the remainder being excreted. The bioavailability of lycopene is greater from tomato paste than from fresh tomatoes. The increased absorption of lycopene from processed products is attributed to the presence of cis isomeric forms [25]. The absorption of lycopene in humans is influenced by several biological and lifestyle factors including gender, age, body mass index and composition, hormonal status, blood lipids concentrations, alcohol consumption, smoking, and the presence of other carotenoids in the consumed products [20]. When lycopene is administered as the all-trans isomer it rapidly isomerizes to a mixture containing more than 50% cis-isomers during absorption in the bloodstream and tissues. Moreover, a study showed that administration of all-trans lycopene in tomato sauce to human subjects for three weeks resulted in 77.3% cis isomers in prostate tissue and thus only 22.7% all-trans lycopene [26]. Liver, seminal vesicles, and prostate tissue are the primary sites of lycopene accumulation in humans [27]. Recent studies indicate that the accumulation in these sites may be due to the involvement of an active process for the uptake of carotenoids via the scavenger receptor class B type 1 protein (SR-B1) transporter, in addition to passive diffusion [28]. The full metabolic routes of lycopene in humans is still unclear. Only a few metabolites, such as 5,6-dihydroxy-5,6-dihydro-lycopene, have been detected in human plasma. It is suggested that lycopene may undergo in vivo oxidation to form epoxides which then may be converted to the polar 5,6-dihydoxy-5,6-dihydro-lycopene through metabolic reduction [29].

1.2.3. Mechanism of Action (In Vitro)

Lycopene has been shown to inhibit the binding abilities of NF-κB and stimulatory protein-1 (SP1), and decreased expression of insulin-like growth factor-1 receptor (IGF-1R) and intracellular ROS concentrations in human SK-Hep-1 cells [30]. Recently, Fenni et al. [31] confirmed the potential involvement of lycopene in decreasing the binding abilities of NF-κB. They demonstrated the ability of lycopene supplementation to inhibit high-fat diet-induced

obesity, inflammatory response, and associated metabolic disorder in mice. They evaluated the effect of lycopene on the phosphorylation of p65 and IκB, which are involved as modulators in the NF-κB pathway. Lycopene was able to strongly reduce phosphorylation of p65 and IκB, resulting in the deactivation of the NF-κB pathway, that previously was induced by the consumption of a high-fat diet. This effect can thus be seen as the induction of an anti-inflammatory effect. These results have also been observed in SW480 human colorectal cancer cells, where lycopene restrained NF-κB and JNK activation, resulting in a suppression of TNF-α, IL-1β, IL-6, COX-2, and iNOS expression. However, relatively high concentrations of lycopene were used (10–30 μM) compared to usual detectable plasma levels (1–2 μM) [32]. While in vitro and animal studies show promise for the potential health effects of lycopene, the relationship between lycopene and low-grade chronic inflammation in itself has so far been inconclusive in humans. Various systematic reviews have already been conducted on lycopene and how it affects different diseases and their symptoms, such as prostate and bladder cancer, Cardiovascular risk and metabolic syndrome [33][34][35][36]. The cross-sectional and intervention studies assessed in these reviews were often inconclusive, and the inconsistency among studies and the type of lycopene tested makes comparison difficult. The different lycopene measurements (self-reported FFQ, measurement of product, circulating lycopene) are a possible reason for the inconsistent results. Circulating measures are preferred for assessing relations, because self-reported measures of lycopene intake are subject to recall bias or memory error and intake measurements do not provide insight in the absorption, distribution, metabolism, and excretion of lycopene in the body. For in vivo studies, however, it is necessary to not just focus on lycopene intake but to actually measure the circulating lycopene concentrations in plasma or serum, in order to understand the health effects on humans [21]. C-reactive protein (CRP) and interleukin-6 (IL-6) are most commonly used to measure inflammation, but some studies have reviewed other inflammatory biomarkers (hyaluronic acid (HA), malondialdehyde (MDA), adiponectin, monocyte chemoattractant protein 1 (MCP-1), thiobarbituric acid reactive substances (TBARS), serum amyloid A (SAA), tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β)). These will also be included in this study [37][38].

2. Discussion

This is, to our knowledge, the first systematic review to assess the correlation and causation between circulating lycopene (the bioavailable lycopene following consumption) and low-grade chronic inflammation. This review reveals that there is strong evidence indicating that lower circulating lycopene concentrations are related with higher inflammation biomarkers in patients with various diseases. In addition, this systematic review shows that there is little evidence that tomato intake or lycopene supplementation diminishes this inflammation.In only one of the five studies in which CRP or lycopene levels were arranged into tertiles/quartiles, no association was found between circulating lycopene and CRP [39][40][41][42][43]. This could be attributable to the low CRP levels of the studied young adults (18–30); all mean CRP levels measured were between 0.99 and 1.11 mg/L [41]. On the contrary, the results from another study [40] showed a significant association and measured high-sensitivity CRP (hs-CRP) ranging from 0.80 and 1.27 mg/L. Moreover, when comparing the corresponding lycopene levels, it is striking that the values of Hozawa et al. [41] lie between 0.0242 and 0.0918 μmol/L, whereas most lycopene levels measured in all studies are between 0.1 and 1 μmol/L. It is therefore also possible that a non-reliable lycopene measurement has been carried out, so that no association could be found. The other three studies [39][42][43] did

confirm the findings of Kim et al. [40], so there is strong evidence to suggest an association between circulating lycopene and CRP.The eighteen studies evaluating the relationship between circulating lycopene and inflammation in healthy participants and patients gave similar results. These studies found lower circulating lycopene concentrations coincide with higher inflammation biomarkers in patients suffering from various diseases. These comparable results suggest that lycopene levels are adversely affected during inflammation and disturbed homeostasis. One possible explanation is that the development of oxidative stress during inflammation is responsible for the decreased lycopene levels. The prooxidant–antioxidant imbalance that ensues during oxidative stress may result in the increased utilization of endogenous and exogenous antioxidants, depleting circulating antioxidant concentrations. For that reason, any protective association that exists between serum lycopene and inflammation in patients may be attenuated [44][45][46][47]. Although the mechanisms underpinning reduced lycopene levels during inflammation are not fully elucidated, depletion of lycopene may be in part the first sign of low-grade inflammation.Seventeen intervention studies were identified which better elucidate this carotenoid's causal effect on inflammation and outcomes. Results from cross-sectional studies preclude the ability to ascribe causality because of both potential confounding and a lack of knowledge about the temporal relation between variables of interest. Most studies successfully increased lycopene levels through supplementation or tomato intake. In one study, supplementation with Lactolycopene capsules did not significantly increase lycopene levels. The authors emphasized the importance of proper supplement development, as another supplement increased circulating lycopene. In addition, supplementation with a combination of lycopene and rosuvastatin did not increase lycopene levels either [48]. The latter result could be explained by another study, in which supplementation with simvastatin, a comparable statin, led to a decrease in circulating lycopene. However, lycopene levels per total cholesterol were significantly increased following simvastatin treatment. The observed change in carotenoid status during simvastatin treatment was mainly attributed to the decrease in cholesterol, emphasizing the importance of cholesterol adjustment for expressing carotenoid levels [49]. This work found that the effect of lycopene supplementation or tomato intake on inflammation is incongruent: no changes in inflammation biomarkers were observed in half of the studies, and in the other half not all results were in line. Inflammatory markers were not altered by lycopene in moderately overweight or obese people, despite the significant increase in circulating lycopene after supplementation [50][51][52]. Intervention studies in patients with Cardiovascular disease or type 2 diabetes also showed minimal reduction of inflammatory markers [53][54][55][56]. In some intervention studies, it was stated that the intervention period was too short to observe a decrease in inflammatory biomarkers in patients. However, previous research has shown that treatment with non-steroidal anti-inflammatory drugs (NSAIDs) for a short period (two weeks) may reduce inflammatory biomarkers in patients, so these inflammatory biomarkers are unlikely to take longer to decrease [57][58]. Likewise, the results of lycopene supplementation in healthy participants were also inconsistent. Only two studies observed a significant decrease in hs-CRP after high lycopene supplementation (15 mg/day) or tomato sauce (sofrito) intake [59], but no effects were found after low lycopene supplementation (6 mg/day) [60] nor 7 mg/day [55]. The hs-CRP test accurately measures low CRP levels to identify low but persistent inflammatory levels. Therefore, it is more suitable for studying low-grade chronic inflammation in healthy participants in further research. However, it is debatable whether such a significant reduction in CRP below the standard values of 1–3 mg/L is clinically relevant and shows an actual anti-inflammatory effect, as these low CRP values already demonstrate that there is hardly any inflammation present. The other studies evaluating CRP

report no significant changes in CRP levels following lycopene intake, probably because of the already low basal value in healthy participants. In addition, it would be of interest to evaluate new, more sensitive biomarkers in subsequent studies, as MCP-1 and adiponectin prove to be suitable biomarkers to study inflammation in healthy subjects [61]. Two intervention studies investigated the potential beneficial effects of lycopene in its isolated form (supplement) and via a lycopene-rich diet. These particular studies showed that both methods were successful in increasing circulating lycopene, but not in changing inflammation biomarkers [50][52]. These results suggest that the form in which lycopene is administered is of less importance than the absorption per se. For example, the absorption of lycopene can be improved by method of preparation such as adding olive oil [62]. Current literature indicates that the incorporation of a functional food with the compound of interest could potentially enhance these protective properties through the provision of an intact food matrix. However, more research is needed to elucidate these speculations. The matrix may provide a synergistic environment to promote the bioactivity of phytonutrients. However, this matrix also presents a challenge, since the direct effects of lycopene cannot be separated from other bioactive compounds within the food [63][64].

3. Conclusions

The available evidence indicates that lycopene levels are adversely affected during inflammation and homeostatic imbalance. Although the mechanisms underpinning these reduced lycopene levels are not fully elucidated, depletion of lycopene may be one of the first signs of low-grade inflammation. Even though supplementation with lycopene or an increased intake of tomatoes does result in an increase in circulating lycopene, there is little evidence that the lycopene increase also results in relieving this inflammation. This phenomenon, also known as the "antioxidant paradox," limits the added value of lycopene supplementation in both patients and healthy individuals.

References

1. Georgiou, N.; Garssen, J.; Witkamp, R. Pharma–nutrition interface: The gap is narrowing. Eur. J. Pharmacol. 2011, 651, 1–8.
2. Bagetta, D.; Maruca, A.; Lupia, A.; Mesiti, F.; Catalano, R.; Romeo, I.; Moraca, F.; Ambrosio, F.; Costa, G.; Artese, A.; et al. Mediterranean products as promising source of multi-target agents in the treatment of metabolic syndrome. Eur. J. Med. Chem. 2020, 186, 111903.
3. Kashi, D.; Shabir, A.; Da Boit, M.; Bailey, S.; Higgins, M. The Efficacy of Administering Fruit-Derived Polyphenols to Improve Health Biomarkers, Exercise Performance and Related Physiological Responses. Nutrients 2019, 11, 2389.
4. Maria, L.; Eamon, E.; Mana, S.; Rosa, C. Relation of Fruits and Vegetables with Major Cardiometabolic Risk Factors, Markers of Oxidation, and Inflammation. Nutrients 2019, 11, 2381.

5. Bosma-den Boer, M.; van Wetten, M.; Pruimboom, L. Chronic inflammatory diseases are stimulated by current lifestyle: How diet, stress levels and medication prevent our body from recovering. Nutr. Metab. 2012, 9, 32.
6. de Boer, A.; van de Worp, W.; Hageman, G.; Bast, A. The effect of dietary components on inflammatory lung diseases–a literature review. Int. J. Food Sci. Nutr. 2017, 68, 771–787.
7. Ruiz-Núñez, B.; Pruimboom, L.; Dijck-Brouwer, D.; Muskiet, F. Lifestyle and nutritional imbalances associated with Western diseases: Causes and consequences of chronic systemic low-grade inflammation in an evolutionary context. J. Nutr. Biochem. 2013, 24, 1183–1201.
8. Todoric, J., Antonucci, L. and Karin, M., Targeting Inflammation in Cancer Prevention and Therapy. Cancer Prevention Research, 2016, 9(12), pp.895-905. Medzhitov, R. Inflammation 2010: New Adventures of an Old Flame. Cell 2010, 140, 771–776.
9. Calder, P.; Ahluwalia, N.; Albers, R.; Bosco, N.; Bourdet-Sicard, R.; Haller, D.; Holgate, S.; Jönsson, L.; Latulippe, M.; Marcos, A.; et al. A Consideration of Biomarkers to be Used for Evaluation of Inflammation in Human Nutritional Studies. Br. J. Nutr. 2013, 109, S1–S34.
10. Chen, L.; Deng, H.; Cui, H.; Fang, J.; Zuo, Z.; Deng, J.; Li, Y.; Wang, X.; Zhao, L. Inflammatory responses and inflammation-associated diseases in organs. Oncotarget 2017, 9, 7204–7218.
11. Del Giudice, M.; Gangestad, S. Rethinking IL-6 and CRP: Why they are more than inflammatory biomarkers, and why it matters. Brain Behav. Immun. 2018, 70, 61–75.
12. Minihane, A.; Vinoy, S.; Russell, W.; Baka, A.; Roche, H.; Tuohy, K.; Teeling, J.; Blaak, E.; Fenech, M.; Vauzour, D.; et al. Low-grade inflammation, diet composition and health: Current research evidence and its translation. Br. J. Nutr. 2015, 114, 999–1012.
13. Lacourt, T.; Vichaya, E.; Chiu, G.; Dantzer, R.; Heijnen, C. The High Costs of Low-Grade Inflammation: Persistent Fatigue as a Consequence of Reduced Cellular-Energy Availability and Non-adaptive Energy Expenditure. Front. Behav. Neurosci. 2018, 12, 78.
14. Liu, C.; Abrams, N.; Carrick, D.; Chander, P.; Dwyer, J.; Hamlet, M.; Macchiarini, F.; PrabhuDas, M.; Shen, G.; Tandon, P.; et al. Biomarkers of chronic inflammation in disease development and prevention: Challenges and opportunities. Nat. Immunol. 2017, 18, 1175–1180.
15. Mendes, A.; Cruz, M.; Gualillo, O. Editorial: The Physiology of Inflammation—The Final Common Pathway to Disease. Front. Physiol. 2018, 9, 1741.
16. Kaluza, J.; Håkansson, N.; Harris, H.; Orsini, N.; Michaëlsson, K.; Wolk, A. Influence of anti-inflammatory diet and smoking on mortality and survival in men and women: Two prospective cohort studies. J. Int. Med. 2018, 285, 75–91.
17. Khoo, H.; Prasad, K.; Kong, K.; Jiang, Y.; Ismail, A. Carotenoids and Their Isomers: Color Pigments in Fruits and Vegetables. Molecules 2011, 16, 1710–1738.

18. Schieber, A.; Carle, R. Occurrence of carotenoid cis-isomers in food: Technological, analytical, and nutritional implications. Trends Food Sci. Technol. 2005, 16, 416–422.
19. Rao, A.; Ray, M.; Rao, L. Lycopene. Adv. Food Nutr. Res. 2006, 51, 99–164.
20. Palozza, P.; Parrone, N.; Catalano, A.; Simone, R. Tomato Lycopene and Inflammatory Cascade: Basic Interactions and Clin.Implications. Curr. Med. Chem. 2010, 17, 2547–2563.
21. Di Mascio, P.; Kaiser, S.; Sies, H. Lycopene as the most efficient biological carotenoid singlet oxygen quencher. Arch. Biochem. Biophys. 1989, 274, 532–538.
22. Parker, R. Absorption, metabolism, and transport of carotenoids. FASEB J. 1996, 10, 542–551.
23. Stahl, W.; Sies, H. Lycopene: A Biologically Important Carotenoid for Humans? Arch. Biochem. Biophys. 1996, 336, 1–9.
24. Gärtner, C.; Stahl, W.; Sies, H. Lycopene is more bioavailable from tomato paste than from fresh tomatoes. Am. J. Clin. Nutr. 1997, 66, 116–122.
25. van Breemen, R.; Xu, X.; Viana, M.; Chen, L.; Stacewicz-Sapuntzakis, M.; Duncan, C.; Bowen, P.; Sharifi, R. Liquid Chromatography−Mass Spectrometry of cis
26. van Breemen, R.; Xu, X.; Viana, M.; Chen, L.; Stacewicz-Sapuntzakis, M.; Duncan, C.; Bowen, P.; Sharifi, R. Liquid Chromatography−Mass Spectrometry of cis and all-trans-Lycopene in Human Serum and Prostate Tissue after Dietary Supplementation with Tomato Sauce. J. Agric. Food Chem. 2002, 50, 2214–2219.
27. Zaripheh, S.; Erdman, J. The Biodistribution of a Single Oral Dose of [14C]-Lycopene in Rats Prefed Either a Control or Lycopene-Enriched Diet. J. Nutr. 2005, 135, 2212–2218.
28. Wang, X. Lycopene metabolism and its biological significance. Am. J. Clin. Nutr. 2012, 96, S1214–S1222.
29. Nagao, A. Oxidative Conversion of Carotenoids to Retinoids and Other Products. J. Nutr. 2004, 134, S237–S240.
30. Huang, C.; Fan, Y.; Lin, C.; Hu, M. Lycopene inhibits matrix metalloproteinase-9 expression and down-regulates the binding activity of nuclear factor-kappa B and stimulatory protein-1. J. Nutr. Biochem. 2007, 18, 449–456.
31. Fenni, S.; Hammou, H.; Astier, J.; Bonnet, L.; Karkeni, E.; Couturier, C.; Tourniaire, F.; Landrier, J. Lycopene and tomato powder supplementation similarly inhibit high-fat diet induced obesity, inflammatory response, and associated metabolic disorders. Mol. Nutr. Food Res. 2017, 61, 1601083.
32. Cha, J.; Kim, W.; Ha, A.; Kim, M.; Chang, M. Anti-inflammatory effect of lycopene in SW480 human colorectal cancer cells. Nutr. Res. Pract. 2017, 11, 90.

33. Senkus, K.; Tan, L.; Crowe-White, K. Lycopene and Metabolic Syndrome: A Systematic Review of the Literature. Adv. Nutr. 2018, 10, 19–29.

34. Cheng, H.; Koutsidis, G.; Lodge, J.; Ashor, A.; Siervo, M.; Lara, J. Tomato and lycopene supplementation and Cardiovasc. risk factors: A systematic review and meta-analysis. Atherosclerosis 2017, 257, 100–108.

35. Rowles, J.; Ranard, K.; Smith, J.; An, R.; Erdman, J. Increased dietary and circulating lycopene are associated with reduced prostate cancer risk: A systematic review and meta-analysis. Prostate Cancer Prostatic Dis. 2017, 20, 361–377.

36. Wu, S.; Liu, Y.; Michalek, J.; Mesa, R.; Parma, D.; Rodriguez, R.; Mansour, A.; Svatek, R.; Tucker, T.; Ramirez, A. Carotenoid Intake and Circulating Carotenoids Are Inversely Associated with the Risk of Bladder Cancer: A Dose-Response Meta-analysis. Adv. Nutr. 2019, 11, 630–643.

37. Nakkeeran M.; Periasamy S.; Inmozhi S.R.; Santha K.; Sethupathy S. Increased Levels of Inflammatory Marker hsCRP, MDA and Lipid Profile in Non-obese Hypertension Subjects. Anal. Biochem. 2017, 6, 4

38. Zhang, Y.; Zhang, J.; Sheng, H.; Li, H.; Wang, R. Acute phase reactant serum amyloid A in inflammation and other diseases. Adv. Clin.Chem. 2019, 90, 25–80.

39. Mazidi, M.; Kengne, A.; Katsiki, N.; Mikhailidis, D.; Banach, M. Inverse association between serum antioxidant levels and inflammatory markers is moderated by adiposity: A report based on a large representative population sample of American adults. Br. J. Nutr. 2018, 120, 1272–1278.

40. Kim, O.; Yoe, H.; Kim, H.; Park, J.; Kim, J.; Lee, S.; Lee, J.; Lee, K.; Jang, Y.; Lee, J. Independent inverse relationship between serum lycopene concentration and arterial stiffness. Atherosclerosis 2010, 208, 581–586.

41. Hozawa, A.; Jacobs, D.; Steffes, M.; Gross, M.; Steffen, L.; Lee, D. Relationships of Circulating Carotenoid Concentrations with Several Markers of Inflammation, Oxidative Stress, and Endothelial Dysfunction: The Coronary Artery Risk Development in Young Adults (CARDIA)/Young Adult Longitudinal Trends in Antioxidants (YALTA) Study. Clin.Chem. 2007, 53, 447–455.

42. Kritchevsky, S.; Bush, A.; Pahor, M.; Gross, M. Serum Carotenoids and Markers of Inflammation in Nonsmokers. Am. J. Gastroenterol. 2000, 152, 1065–1071.

43. Boosalis, M.; Snowdon, D.; Tully, C.; Gross, M. Acute phase response and plasma carotenoid concentrations in older women: Findings from the nun study. Nutrition 1996, 12, 475–478.

44. Dandekar, A.; Mendez, R.; Zhang, K. Cross Talk Between ER Stress, Oxidative Stress, and Inflammation in Health and Disease. Methods Mol. Biol. 2015, 205–214.

45. Furukawa, S.; Fujita, T.; Shimabukuro, M.; Iwaki, M.; Yamada, Y.; Nakajima, Y.; Nakayama, O.; Makishima, M.; Matsuda, M.; Shimomura, I. Increased oxidative stress in obesity and its impact

on metabolic syndrome. J. Clin. Investig. 2004, 114, 1752–1761.

46. Langham, M.; Zhou, Y.; Chirico, E.; Magland, J.; Sehgal, C.; Englund, E.; Mohler, E.; Guo, W.; Barhoum, S.; Wehrli, F. Effects of age and smoking on endothelial function assessed by quantitative Cardiovasc. magnetic resonance in the peripheral and central vasculature. J.Cardiovasc. Magn. Reson. 2015, 17, 1.
47. Amirkhizi, F.; Siassi, F.; Minaie, S.; Djalali, M.; Rahimi, A.; Chamari, M. Is obesity associated with increased plasma lipid peroxidation and oxidative stress in women? ARYA Atheroscler. 2010, 2, 189–192.
48. Williams, E.; Baines, K.; Smart, J.; Gibson, P.; Wood, L. Rosuvastatin, lycopene and omega-3 fatty acids: A potential treatment for systemic inflammation in COPD; a pilot study. JNIM 2016, 5, 86–95.
49. Rydén, M.; Leanderson, P.; Kastbom, K.; Jonasson, L. Effects of simvastatin on carotenoid status in plasma. Nutr. Metab. Cardiovasc. Dis. 2012, 22, 66–71.
50. McEneny, J.; Wade, L.; Young, I.; Masson, L.; Duthie, G.; McGinty, A.; McMaster, C.; Thies, F. Lycopene intervention reduces inflammation and improves HDL functionality in moderately overweight middle-aged individuals. J. Nutr. Biochem. 2013, 24, 163–168.
51. Markovits, N., Ben Amotz, A.; Levy, Y. The effect of tomato-derived lycopene on low carotenoids and enhanced systemic inflammation and oxidation in severe obesity. Isr. Med. Assoc. J. 2009,11, 598–601.
52. Thies, F.; Masson, L.; Rudd, A.; Vaughan, N.; Tsang, C.; Brittenden, J.; Simpson, W.; Duthie, S.; Horgan, G.; Duthie, G. Effect of a tomato-rich diet on markers of Cardiovasc. disease risk in moderately overweight, disease-free, middle-aged adults: A randomized controlled trial. Am. J. Clin. Nutr. 2012, 95, 1013–1022.
53. Biddle, M.; Lennie, T.; Bricker, G.; Kopec, R.; Schwartz, S.; Moser, D. Lycopene Dietary Intervention. J. Cardiovasc. Nurs. 2015, 30, 205–212.
54. Petyaev, I.; Dovgalevsky, P.; Klochkov, V.; Chalyk, N.; Pristensky, D.; Chernyshova, M.; Udumyan, R.; Kocharyan, T.; Kyle, N.; Lozbiakova, M.; Bashmakov, Y. Effect of lycopene supplementation on Cardiovasc. parameters and markers of inflammation and oxidation in patients with coronary vascular disease. Food Sci. Nutr. 2018, 6, 1770–1777.
55. Gajendragadkar, P.; Hubsch, A.; Mäki-Petäjä, K.; Serg, M.; Wilkinson, I.; Cheriyan, J. Effects of Oral Lycopene Supplementation on Vascular Function in Patients with Cardiovasc. Disease and Healthy Volunteers: A Randomised Controlled Trial. PLoS ONE 2014, 9, e99070.
56. Upritchard, J.; Sutherland, W.; Mann, J. Effect of supplementation with tomato juice, vitamin E, and vitamin C on LDL oxidation and products of inflammatory activity in type 2 diabetes. Diabetes Care 2000, 23, 733–738.

57. Yan, Y.; Guo, T.; Zhu, C. Effects of nonsteroidal anti-inflammatory drugs on serum proinflammatory cytokines in the treatment of ankylosing spondylitis. Biochem. Cell Biol. 2018, 96, 450–456.
58. Gallelli, L.; Galasso, O.; Falcone, D.; Southworth, S.; Greco, M.; Ventura, V.; Romualdi, P.; Corigliano, A.; Terracciano, R.; Savino, R.; Gulletta, E.; et al. The effects of nonsteroidal anti-inflammatory drugs on Clin.outcomes, synovial fluid cytokine concentration and signal transduction pathways in knee osteoarthritis. A randomized open label trial. Osteoarthr. Cartil. 2013, 21, 1400–1408.
59. Hurtado-Barroso, S.; Martínez-Huélamo, M.; Rinaldi de Alvarenga, J.; Quifer-Rada, P.; Vallverdú-Queralt, A.; Pérez-Fernández, S.; Lamuela-Raventós, R. Acute Effect of a Single Dose of Tomato Sofrito on Plasmatic Inflammatory Biomarkers in Healthy Men. Nutrients 2019, 11, 851.
60. Kim, J.; Paik, J.; Kim, O.; Park, H.; Lee, J.; Jang, Y.; Lee, J. Effects of lycopene supplementation on oxidative stress and markers of endothelial function in healthy men. Atherosclerosis 2011, 215, 189–195.
61. Li, Y.; Chang, Y.; Huang, H.; Wu, Y.; Yang, M.; Chao, P. Tomato juice supplementation in young women reduces inflammatory adipokine levels independently of body fat reduction. Nutrition 2015, 31, 691–696.
62. Fielding, J.M.; Rowley, K.G.; Cooper, P.; O' Dea, K. Increases in plasma lycopene concentration after consumption of tomatoes cooked with olive oil. Asia Pac. J. Clin. Nutr. 2005, 14, 131–136.
63. Raikos, V. Food matrix: Natural barrier or vehicle for effective delivery of carotenoids from processed foods? Nutr. Metabol. Insights 2017, 1, 1-6.
64. Crowe, K. M. Designing Functional Foods with Bioactive Polyphenols: Highlighting Lessons Learned from Original Plant Matrices. J. Hum. Nutr. Food Sci. 2014, 1, 1018.