Review Article

A Review on Natural Pigment Lycopene with its Promising Effect in Chronic Diseases

Sanjay Kisan Metkar
Assistant Professor, Department of Biotechnology, Badrinarayan Barwale Mahavidyalaya, Chandanzira, Jalna, Maharashtra 431213, India.

Dr. Sanjay Metkar completed PhD in Medical Biotechnology from Chettinad Academy of Research and Education, Chennai. Presently he is working as Assistant Professor in Department of Biotechnology and his area of interest is on Protein aggregation and its inhibitors from natural sources.

Corresponding author - DR. Sanjay Kisan Metkar (geneclone7@gmail.com)

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Abstract

Lycopene is a bioactive compound primarily found in tomato. It is described by an agent with high cancer prevention potential. Predominantly because of this property, lycopene has been recommended to show numerous advantageous impacts, including its potential as anti-cancerand cardio protective agent. The studies suggested that the consumption lycopene in food or by itself may reduce cancer and cardiovascular disease risk. However, there are insufficient clinical trial data to support the hypothesis.It acts by multiple mechanisms including the regulation of growth factor signaling, cell cycle arrest and/or apoptosis induction, metastasis and angiogenesis, as well as by modulating the anti-inflammatory and phase II detoxification enzymes activities.In this review, the anti-cancer and cardioprotective properties of lycopene are discussed.

Keywords: Lycopene, Cancer, Cardiovascular disease, Antioxidant, Anti-inflammatory

Introduction

Free radicals of oxygen and less consumption of green vegetables and seasonal fruits are the major reasons to provoke human ailments and disturbs human immunity.[1] Presently the dietary guidelines are suggesting that more intake of green vegetables and fruits in diet which comes with high content of antioxidants leads to overcome the chronic diseases like cancer, and coronary artery diseases.[2] Tomato is one of the vegetable which is a common part of diet of all people in the world and its influence in the health sector has been recognized in various studies.[3] Lycopene is one of the important content found in tomato which has promising effects in human diseases.[4] The importance of lycopene in human nutrition and prevention of disease made lycopene as one of the strongest antioxidant among carotenoids after astaxanthin. The ability of lycopene as an antioxidant have shown strong ability to scavenge and quench reactive oxygen species (ROS).[5] Lycopene is one of the most intense antioxidant, with a singlet-oxygen-extinguishing capacity twice as high as that of β-carotene and multiple times higher than that of α-tocopherol.[6] It is the most transcendent carotenoid in human plasma and its level is influenced by a few lifestyle and biological factors.Inferable from their lipophilic nature, lycopene and different carotenoids are found to pack in low-density and very low-density lipoprotein parts of the serum. Lycopene is found to be concentrate in the adrenal organ, testicles, liver and prostate organ, where it is the most

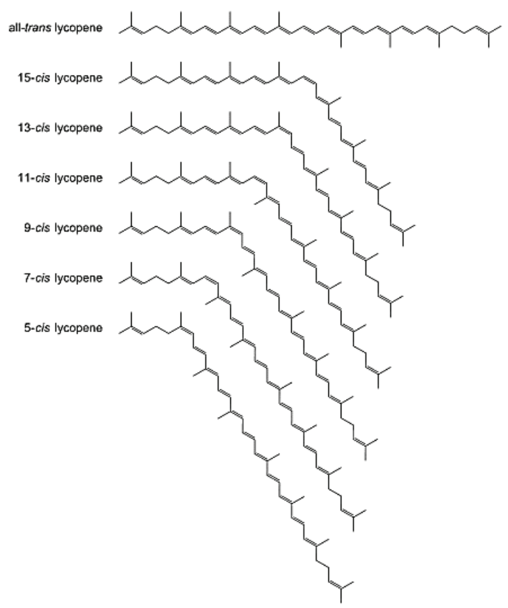

Figure 1: Geometrical isomers of lycopene.8

unambiguous carotenoid.[7] Lycopene is a profoundly unsaturated hydrocarbon containing 11 conjugated and 2 unconjugated double bonds. As a polyene it also experiences cis-trans isomerization prompted by light, thermal energy and chemical reaction. The structure of cis and trans lycopene has shown in Fig 1. Lycopene from natural plant sources exists predominantly in an all-trans configuration, the most thermodynamically stable form.In human plasma, lycopene is present as an isomeric mixture, with 50% as cis isomers.[8]

Role of lycopene in Chronic diseases

The biological activity of carotenoids, for instance, β-carotene possess thepotential to synthesize vitamin A inside the body. Since lycopene doesn't have β-ionone ring structure, it can't synthesize vitamin A. Its biological effect in humans therefore has been credited to mechanism where it is not related to vitamin A synthesis pathway. So, there are some hypothesis related to lycopene where it has been proposed to explain the anticarcinogenic and antiatherogenic activity of lycopene: nonoxidative and oxidative pathways. The hypothesis depicting the role of the lycopene in prevention of several diseases has been summarized in Fig 2. 6

Lycopene's role in cancer

Carotenoid-rich foods have been associated with reduced risk of cancer, such as the prostate and other cancers by various mechanisms. Incorporating the nonoxidative system, the anticancer effect of lycopene has been evidenced in regulation of gap-junction communication in mouse cells fibroblast embryo cells.[8] Lycopene has also a role in suppression of carcinogen induced regulatory proteins like p53 and Rb which may stop cell division at G0-G1 cell cycle phase.[10] Several mechanisms of action have been proposed to explain the anticarcinogenic action ofLycopene as shown in Fig 3.

These include: (i) the inhibition of cancer cell proliferation and induction of differentiation(of cancer cells) by modulating the expression of cell cycle regulatory proteins, (ii) modulation ofthe IGF-1/IGFBP-3 system, (iii) inhibition of oxidative DNA damage, (iv) modulation of redox signaling, (v) upregulation of gap-junctional gene connexin 43 (Cx43) and increased gap junctionalintercellular communication, (vi) inhibition of 5-lipoxygenase, (vii) modulation of carcinogenicmetabolizing enzymes, (viii) modulation of immune function, (ix) modulation of IL-6 and androgen, (x) inhibition of IL-6 and androgen, (xi) inhibition of 5-lipoxygenase,

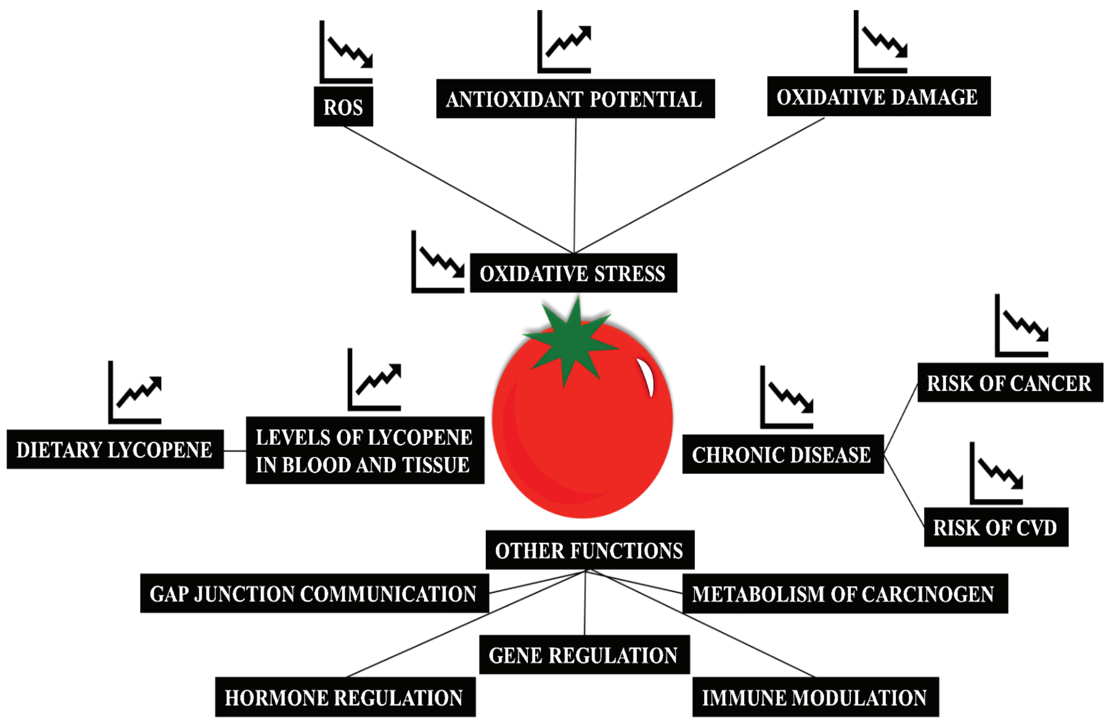

Figure 2: Proposed hypothesis for the role of lycopene in combating chronic diseases. Dietary lycopene may elevate the lycopene concentration in the body and, stand-in as an antioxidant, may catch ROS i.e., reactive oxygen species, elevate the overall antioxidant ability or decrease the oxidative damage to lipid like lipoproteins and membrane lipids, proteins (such as vital enzymes) and DNA (geneticmaterial), thereby reducing oxidative stress. This decreased oxidative stress may lead to less risk for cancer and cardiovascular disease. On the other hand, the elevated lycopene concentration in the body may control functions of gene, expand intercell communication, control hormone and immune response, or regulate metabolism, thus decreasing the risk for chronic disease. These mechanisms may also be unified and may function at the same time to deliver health benefits.[6]

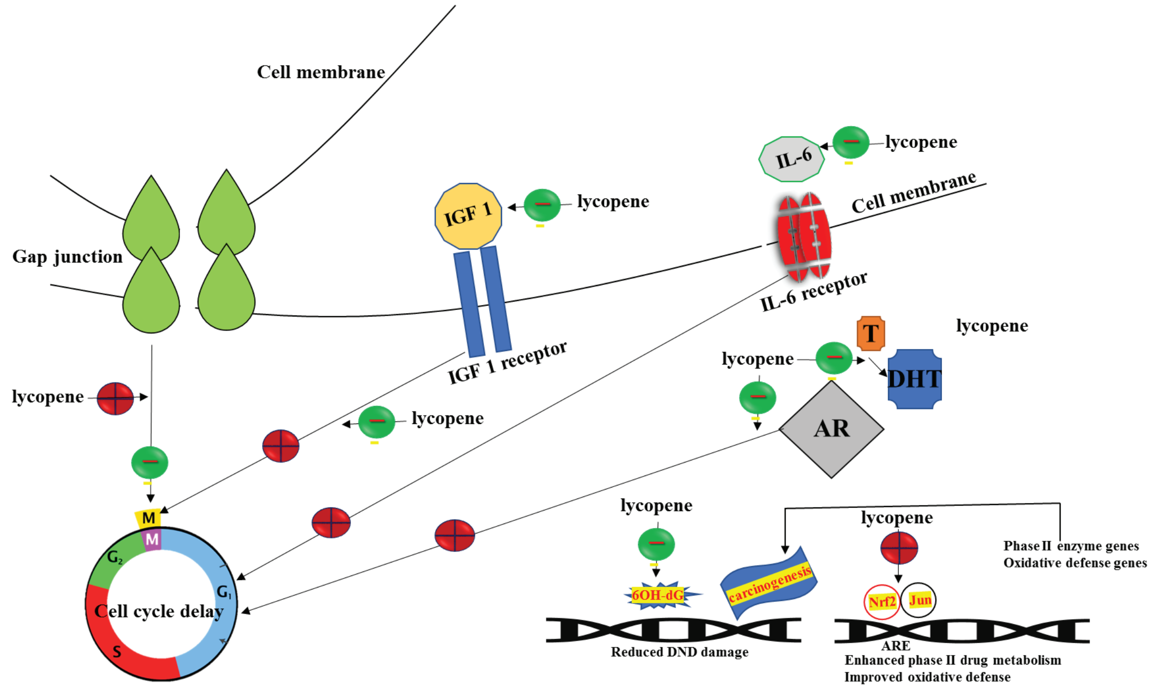

Figure 3: Several molecular and cellular mechanisms of action of lycopene in cancer inhibition.12

(xii) modulation of carcinogen metabolizing enzymes and (xiii) modulation of immune function,[11] (xiv) reduction ofoxidative stress by modulating ROS-producing enzymes (CYP-P450 enzymes, NADPH oxidase, iNOS, COX-2 and 5-LOX), (xv) inducing antioxidant/detoxifying phase II enzymes (also chemical interaction with radioactive materi-als), NQO1 and GST,[12] (xvi) regulation of nuclear factorE2-related factor 2-antioxidant response element (Nrf2-ARE) system,[13] and (xvii) inactiva-tionof growth factor (PDGF, VEGF and IGF)-induced PI3K/AKT/PKB and Ras/RAF/MAPK signaling pathways.[14]

Prostate cancer

Prostate cancer is the second most common cancer and fifth leading cause of death in men. The preventive role of lycopene in prostate cancer have been extensively studied. The inverse correlation of among the prostate cancer and concentration of lycopene in plasma [0.17, odds ratio; 0.005, P value] has been observed in less quintiles of consumption.[15] In various in vitro and in vivo studies, the lycopene has been observed to suppress the prostate cancer. It was found that lycopene induces the down regulation expression of protein kinase B (commonly known as AKT2) detected using reverse transcription-quantitative polymerase chain reaction (RT-qPCR) and western blotting and up regulates the miR-let-7f-1 expression in PC3 cells which was detected by using cell proliferation and apoptosis assays in gain and loss-of-function experiments. Re-insertion of miR-let-7f-1 into PC3 cells was capable to hinder cell proliferation and induce apoptosis. Additional exploration has revealed that up-regulation of miR-let-7f-1-targeted AKT2 and AKT2 in PC3 cells can improve the effects induced by miR-let-7f-1.[16] In one study to support the effect of lycopene in prostate cancer, the mice was fed with lycopene in a powder form [10%] or beadlets [0.25%] for 18 weeks and then the serum was analyzed and the concentration of total 5-cis was higher compared to other cis and all trans lycopene. The occurrence of prostate cancer was less in mice which had lycopene in their diet compared to control group for where lycopene was not a part of diet. The significant loss ofβ-carotene 9',10'-oxygenase (BCO2) suggested the inhibition of prostate carcinogenesis, whereas control group did not alter the BCO2 genotype and prostate cancer.[17] In another investigation, the treatment with lycopene with apo-10-lycopenal elevated the BCO2 expression and diminished cell multiplication in androgen-sensitive cell lines, whereas there was no modification in BCO2 expression or cell growth in lycopene androgen-resistant cells. Reclamation of BCO2 articulation in prostate cancer cells prevented cell expansion and colony formation independent of lycopene exposure.[18] Yang et al., investigated that less (4 mg/kg) or more (16 mg/kg) dose of lycopene and a single β-carotene dose (16 mg/kg) weekly twice for 7 weeks sturdily prohibited the growth of tumor, as it was demonstrated by the decreased volume and weight of tumor in the thimeric nude mice administered subcutaneously with human androgen-independent prostate carcinoma PC-3 cells. At the level of high dose, lycopene and β-carotene expressively reduced the expression of PCNA (proliferating cellular nuclear antigen) in tumor tissues and elevated insulin-like growth factor-binding protein-3 levels in the plasma. In addition, lycopene supplementation at high dose level suggestively decreased the vascular endothelial growth factor (VEGF) in the plasma.[19]

A few examinations supporting the connection between utilization of tomato and a decreased occurrence of prostate cancer have originated from the Health Professionals Follow-Up Study. A potential, single blind, placebo controlled, randomized study wasachieved in which 15 of 26 men arranged for radicalprostatectomy for organ confined malignancy were givenlycopene complements, 15 mg twice a day (Lyc–O–Mato2, LycoRed, Beer-Sheva, Israel) for 3 weeks pre-operatively.Sequential measurements confirmed that 22% lycopene elevation in plasma and tissue levels and astatistically significant reduction in prostate specific antigen(PSA) over 3 weeks duration, in those administrated by lycopene. They also found the reduction in tumor volume and further investigation in excised tissue of tumor revealed the decreased level of cellular proliferation biomarkers of prostate cancer and the level of apoptosis and connexin 43 gap junction was found to be amplified.[20, 21] Phase II randomized clinical trial of 15 mg of lycopene supplementation twice a day for 3 days before radical prostatectomy showed a decrease in plasma IGF-I levels, but no significant change in Bax and Bcl-2.[22]

Bladder cancer

In a case-control study comprising 569 bladder cancer cases and 3123 controls, the relative risk for bladder cancer was 1.08, which equated the maximum and lowermost rates of lycopeneconsumption and concluded that dietary or supplemental intake of vitamin A,vitamin C, vitamin E, and dietary intake of folate andcarotenoids are not associated with bladder cancer risk.[23] In another examination associated with plasma micronutrients and bladder cancer risk showed the protective effect carotenoids on bladder cancer and suggested that the bladder cancer can be prevented just through the proper diet which includes lycopene.[24]

Gastric and colorectal cancer

Gastric cancer is one of the most common cancers in the world, following lung, breast and colorectal cancer and the risk factors of gastric cancer include poor diet, smoking, family history, inflammation, and Helicobacter pylori infection. Scientific studies have shown that diet, with antioxidant nutrients, plays vital part in the inhibition of cancer development. In particular, the consumption of lycopene decreases the risk of many cancers.[25] The study investigated the significant amount of reduction in the number of viable cells in HT 29 [adenocarcinoma cells] and T-84 [human colon carcinoma cells] cell lines after 48 h co-incubation with lycopene. Lycopene induced the cell cycle arrest which made less cell viability after 96 h of treatment in comparison tountreated control. The elevated level of apoptosis was also observed in the mentioned cell lines. It was also observed that it had preventive proliferation role in human cancer cell line like HT-29 with 10 μMas IC50 value. Additionally, study also mentioned that there was suppression of Akt activation and non-phosphorylated protein like catenin in human colon cancer cells.[26] Study also demonstrated that there was inhibition of cell growth that was reliant on dose of lycopene which resulted in cell cycle arrest at G0/G1 and G2/M phase and by apoptosis induction. It was also observed that there was a down regulation of Cyclin D1, Bcl-2, and Bcl-x1 expression.[27] In another study, the introduction of tomato powder exhibited regulation of the Nrf2/HO-1 signaling pathway which showed the chemo preventive role of lycopene and the study also reported that there was induction of apoptosis triggered by suppressing the COX-2 (cyclooxygenase-2) expression by NF-κB pathway.[28]

Higher circulating insulin-like growth factor I (IGF-I) concentrations have been associated withelevated risk of cancer.In a randomized, placebo-controlled, double-blind crossover study, lycopene supplementation for almost 8 weeks showed that elevated serum insulin-like growth factor binding protein (IGFBP-1) concentration in both the gender of humans who have more risk for colorectal cancer, thereby showing the protective role of lycopene in colorectal cancer.[29]

Lycopene was also found to be prevent the Helicobacter pylori-induced increases in ROS, 8-Oxo-2'-deoxyguanosine (oxidized derivative of deoxy guanosine result from DNA oxidation) as well as apoptosis by elevating apoptosis regulator BAX gene. Lycopene induced the changes in cell cycle, DNA breaks and activation of ataxia-telangiectasia-mutated (ATM) and Rad3-related (ATR)-mediated DNA damage when exposedto gastric epithelial AGS cells.[30] The consumption of lycopene (50, 100 and 150 mg/kg body weight) in gastric carcinoma-induced rats up-regulated the redox grade and immune activities and was beneficial in dropping the gastric cancer risk.[31]

Renal cancer

Renal cancer is the most common type of cancer that occurs in kidney andits incidence is increasing worldwide. Researchers used renal cancer rat model named as Eker rat which potentially progressed renal tumor leiomyoma and fed them with lycopene in the range of 100 or 200 mg/kg for almost 18 months and then sacrificed and removed the kidneys. The immunohistochemical staining was done for mTOR, phospho-S6 and EGFRin the kidneys and there was decrease of tumor size from 94 % [control] to 65 % [experimental] with was significantly less ($p<0.12$) but the mean number of renal carcinomas were statistically significant for the lycopene treated rats with $p<0.008$ compared tothe untreated group. Additionally, tumor length was also decreased linearly as concentration of lycopene levels was increased in the diet.[32] Oxidative stress has been believed to play vital function in the pathogenesis of renal cancer. A study involved 240 women with renal cancer, and it was found that the lowest intake of lycopene was associated with highest risk of renal cancer. Similar another study also reported that highest intake of lycopene made 39% lowest risk for the renal cancer [hazard ratio, 0.61; 95% confidence interval, 0.39–0.97].[33] One research aimed to find the potential of lycopene in cisplatin induced renal failure in rats. This study comprised of groups which received only cisplatin (7 mg/kg) with 10 days of lycopene (4 mg/kg) administration and 5 days of lycopene followed with cisplatin was injected intraperitoneally as single dose using gavage with corn oil. Lycopene administered group showed preventive effect for the renal failure as nephrotoxicity in plasma as well as kidney tissues was significantly reduced. Overall,the results indicated that the novel antioxidant lycopene was successful in prevention of oxidative stress in rat.[34]

Cardiovascular disease

Cardiovascular diseases (CVD) are positioning top for the premature death and has shown effect in disability of humans worldwide.Diet has been directly linked to progression of CVD and necessary modulation of diet, that is consumption of more fruits and vegetables was the key for the prevention of CVD. Red fruits such as tomato contains huge amount of lycopene with its antioxidant property which has crucial role for the prevention in CVD. There are various factors involved in development of CVD and most of the studies have found thatthere is ameliorationof antioxidant defense with the use of bioactive compound lycopene.[35]

Lycopene in cardiovascular function

A recent study explored the effect of lycopene in CVD function where only human subjects were considered for the lycopene consumption and its beneficial effect on CVD. Overall, it was seen the high consumption of lycopene has positive effects on various parameters such as blood lipids [total-, HDL-, LDL-cholesterol, triglycerides, oxidised-LDL], pressure and endothelial function[flow-mediated dilation (FMD), pulse wave velocity (PWV)]. The overall outcome of the studyproved that promising lycopene based nutritional strategy was effective for the prevention of CVD.[36] Remarkably,significant alterations between various nations were also highlighted, which proposedthat the topographical context and culture may also alter the cardioprotective effectsof lycopene.[37] Meta-analysis study was carried out to investigate the association among high lycopene consumption, its plasma levels and cardiovascular disease.It was concluded that lycopene was related to 17 % lowering the CVD risk when compared with lowest consumption of lycopene.[38] Reduction of cholesterol level and inflammatory response decline in oxidation of biomolecules, the enhancement of cellular communication and elevation of the apoptosis and the antiangiogenic effects were some of the introduced mechanism for lycopene in the prevention of CVD.[39] Several studies demonstrated the positive effect of lycopene in CVD but there was some investigation where they were unsuccessful to prove the association of lycopene consumption and reduce risk of CVD.[40,41,42]

Lycopene in inflammation associated with CVD risk

The anti-inflammatory impact of lycopene has been associated invarious ways wherelycopene couldalter the cellular activities. The increase in lycopene level in the body seemed to be inversely associated with arterial thickness and, putatively, with the risk of atherosclerosis and/or stroke.[43] Additionally, it was also found that lycopene directly protected the oxidative damage of endothelial cells and prevented monocyte endothelium association and aggregation of platelet.[44] Further, lycopene wasshown to suppress the neutrophils oxidation and secretion of cytokines.[45] The growth of smooth muscle, T-lymphocytes and monocyte was down-regulated upon administration of lycopene.[46] Chronic inflammation exemplified by elevated of highly sensitiveC-reactive protein has been added as one of the risk factors for CVD. In a study performed with heart failure patients, lycopene administration encouraged reduction in the C-reactive protein levels in women but had no significant effect in men.[47] From lycopene administration it was found in a study that it improves vasodilation mediated by endothelial cellsin healthy control patients, but no significant effect was observed which may suggest lycopene particularly impacts as a secondary player.[48]

Lycopene renders tremendous amount of antioxidant activity, but in few cases its functions in cardiovascular protection seemed to be highly associated with its anti-inflammatory properties rather than prevention of oxidation of LDL (low density lipoprotein). Due to thehigher hydrophobicity of lycopene, the probability of finding it in the nuclear hydrophobic core ofthe lipoproteinis higher.[49] Moreover, it was recommended that intake of one or more portion/day of tomato rich products is highly associated with 30% lower risk of CVD.[50]

Conclusion

Lycopene which a major component of tomato is found to have a significant role inprevention and alteration of carcinogenic development. Its job in cancer prevention is fully reported and supported with various experiments. Lycopene can be absorbed more productively by the body even after it has been processed into juice, sauce, puree, or ketchup. In new organic products, lycopene is enclosed in fruit tissue. In this manner, just a minute-quantity of the lycopene that is available in fresh fruit is absorbed. Preparing organic product makes the lycopene progressively bioavailable by expanding its surface areawhich is easily accessible for digestion and absorption. Likewise, because lycopene is fat-soluble (as are vitamins A, D, and E and the provitamin beta-carotene), absorption is improved in the presence of oil in the diet. Cancer prevention agents assume a significant job in protecting cells and cell components against oxidative damage. Overall, the research articles reviewed in this review deliver considerable indication signifying a role for lycopene in cancer and CVD. Lycopene may act by various mechanisms, some of which could be related to the antioxidant action of this non-pro-vitamin-A carotenoid. Lycopene supplementation could be a suitable candidate for future clinical trials in various types of cancer and CVD both as a protective and as a therapeutic agent and in combination with other therapies.

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