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Lycopene for Cardiovascular Health: Preclinical to Clinical Evidence

Sunil B. Pandit[1*], Varun V. Joshi1, Sumitkumar M. Sharma[1], Roshan P. Wagh[1], Manojkumar S. Mahajan[1], Aman B. Upaganlawar[1], Chandrashekhar D. Upasani[1], Preeti Meshram[2] ,Vivekanand A. Kashid[3]

[1]Department of Pharmacology, SNJB's Shriman Sureshdada Jain College of Pharmacy, Neminagar, Chandwad, Nashik, Maharashtra, 423101, India.

[2]Department of Pharmaceutics, Sinhgad College of Pharmacy, Vadgaon, Pune, Maharashtra, 411041 India.

[3]Department of Pharmaceutics GSS's Dr. Kolpe Institute of Pharmacy, Kolpewadi, Tal. Kopargaon Dist. Ahmednagar, Maharashtra, 423 602, India.

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ABSTRACT:
Cardiovascular disorder is a significant source of illness and destruction in the US and worldwide. It is well known that diet and cardiovascular disease (CVD) are related and that managing and preventing CVD begins with dietary changes. The latest epoch of nutritional, medicinal, botanical, physiological, and analytical sciences has emerged due to the finding of bioactive constituents behind the necessary supplements appearing in foods. The main metabolic benefits of lycopene include improving the increase of LDL and VLDL and reducing arterial stiffness. It also has anti-atherosclerotic, antioxidant, anti-hypertensive, and lowers the pro-inflammatory cytokines. One food ingredient that has caught the interest of scientists in food, agriculture, and dietary accessory businesses is lycopene. Lycopene positively impacts health, particularly those connected to its antioxidant properties and ability to prevent cardiovascular disease (CVD). In addition to giving tomatoes and tomato-based products their characteristic red shade, lycopene also has health-beneficial qualities. Several preclinical and clinical studies have proven the value of lycopene in treating cardiovascular disease.

1. Introduction

Cardiovascular disorder is the most significant source of morbidity and mortality in humans globally, which is responsible for 32% (17.5 million) of all fatalities worldwide (WHO CVDs, 2019). By 2020, if the diseases continue their current track, there will be close to 25 million fatalities annually [1].

The term "CVD (cardiovascular disease)" refers to a wide variety of illnesses, together including hypertension, valvular and congenital cardiopathy, congestive heart failure (CHF), exterior vascular illness, congestive heart failure (CHF), stroke, and myocardial infarction. The hallmarks of coronary thrombosis sentiment sickness are myocardial infarction (MI), angina pectoris, coronary thrombosis inadequacy, and coronary thrombosis mortality (CHD). Examples of cerebral vascular diseases include transient ischemic attacks and strokes (TIA) [2].

Age and hereditary variables are typically regarded as unchangeable CVD risk factors. However, about of the adaptable influences that consume remained identified by way of the primary source of cardiovascular demise and incapacity remain smouldering, hypertension, abdominal obesity, unusual lipid profiles, diabetes mellitus, trauma, less fruit and vegetable utilization, and irregular physical activity [3,4].

Given that nutrition is implicated in the development of CVD according to evidence from numerous epidemiological studies, dietary modification has attracted considerable interest, and current research is focused on figuring out how to modify one's diet to prevent developing CVD [5]. In this context, health

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professionals frequently advise greater utilization of a regime from top to toe, which is more popular than vegetables as the excellent origin of different antioxidants [6].

Cardiovascular diseases (CVD) are among the most significant social issues worldwide. Subsequently, the incidence and mortality of these diseases are high each year. Figures show that 17.8 mountain fatalities were all-inclusive, which remained produced through CVD in 2019, and that amount remains predicted to increase by nearly 23 mountains by 2030 [7,8].

It is also stated that cardiovascular disease affects young individuals more frequently and that people below 70 account for one-third of all fatalities. Myocardial infarction and stroke are their primary causes [9]. The World Health Organization (WHO) characterizes cardiac illnesses using situations that disturb the sentiment, then body fluid bowls for hypertension, peripheral artery illness, coronary blood vessel illness, and heart failure [10].

Most conditions brought on by atherosclerosis, regardless of location, determine death from cardiovascular diseases. This is considered an oxidative stress-related deteriorating progression of the main barrier that manifests as persistent inflammation [11]. Other cardiovascular illnesses, such as heart failure, involve complicated relationships between the metabolic and molecular alternates, widespread oxidative tension, swelling, fat absorption, and endothelial and myocardial dysfunction that substantially contribute to their development [12].

Cardiovascular disease can occur for a variety of reasons. Rendering toward the American English Culture aimed at Defensive Cardiology (ASPC) 2021, the issue remains unnatural diet, insufficient exercise, dyslipidemia, hyperglycemia, elevated plasma compression, obesity, negotiations of de-tailed residents (elder stage, battle, society, gender), clotting, smoke, dysfunctional kidney illness, and heritable/household hypercholesteremia [13].

CVD danger is suggestively enlarged through a regime of substantial cutting-edge SFA, mint, salty, and little trendy herbal-resultant nutriments, particularly renewed achene and root vegetables [14]. As a result, one of the critical elements that may shield against a Mediterranean diet is reducing the hazard of CVD [15]. The Mediterranean diet (Med Diet), which emphasizes fresh produce and minimally processed foods like olive oil (EVOO), tomatoes, and tomato-based materials, appears to be the best dietary pattern for preserving a healthy circulatory system [16]. In addition to providing essential bioactive components for the body, tomatoes, a staple of the Mediterranean Sea regime, then remain consumed and renewed or treated as per fluids, essences, kinds of ketchup, or other consommes, are similarly very beneficial to human health. Among these include vitamins (ascorbic acid, tocopherol), phenolic compounds (quercetin, kaempferol, and naringenin), and carotenoids (lycopene, β-carotene) [17]. Because of this, tomato materials are essential to researchers whose work focuses on determining whether lycopene utilization and the development of CVD are related [18]. Their extensive epidemiological research offers timely information on lycopene and supports its role in preventing cardiovascular diseases [19]. Lycopene is thought to protect the cardiovascular system and possess anti-cancer assets. It is efficient against breast, lung, stomach, and prostate cancer. More importantly, this substance prevents the growth of cancerous cells, triggers their planned demise, and prevents metastasis. Additionally, lycopene possesses an expert-healthiness solid effect on the skeletal organization. The problem promotes better jaw mineralization than guards in contrast to osteoporosis. The situation also has antiproliferative qualities, which help treat and prevent nervous illnesses similar to Huntington's, Parkinson's, and then Alzheimer's [20]. A natural red pigment called lycopene remnants freshman popular alimentations, namely Lycopersicon esculentum, watermelon vine, glowing Citrus paradisi, Carica papaya, peaches, then Psidium guajava [21].

2. Lycopene and cardiovascular disease

Frequent revisions have been directed toward the last several eras to hazard the potential health advantages of carotenoids, particularly lycopene [22]. Numerous studies have found a correlation between higher blood planes of lycopene in the plasma (blood plasma/serum) and minor jeopardy of cardiac illness, as well as enlarged ingesting of lycopene-amusing nutriments like Lycopersicon esculentum than Lycopersicon esculentum-founded harvests [23].

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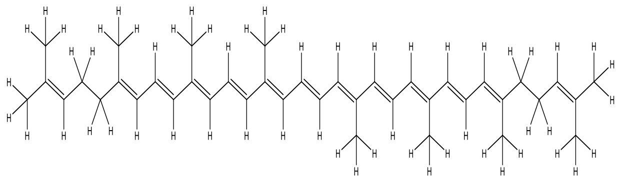
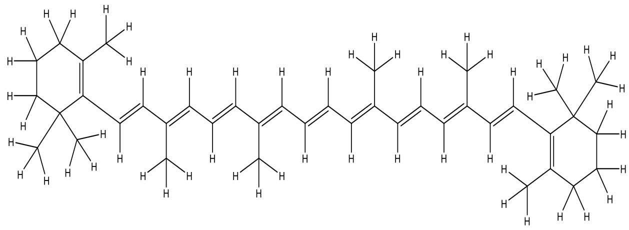
However, lycopene research has attracted much attention due to the inconsistent results of trials, including vitamin E and β-carotene supplementation, regarding CVD. This review examines the effects of lycopene on cardiovascular disease (CVD) and CVD hazard features using data from various studies on people and animals [23].

Lycopene is an unsaturated, lipophilic, physiologically active acyclic carotenoid [24]. The absence of the proper enzymes prohibits lycopene from acting as a provitamin A precursor in the human diet, even though it is considered an essential stage in the carotenoid synthesis process in plants. Plant lycopene is mainly found in its all-trans isomer [25]. Associate toward positive, then-current enthusiasm causes the altogether-trans isomer to isomerise fanatical by the additional bioavailable cis-isomer trendy acid circumstances (such as stomach acid) [26]. The antioxidant lycopene remains accountable aimed at the enflamed hue of Lycopersicon esculentum, watermelons, papayas, red grapefruits, apricots, and guavas [27, 28].

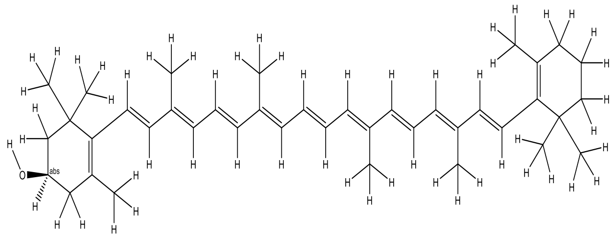
The fruit's lycopene content increases throughout ripening. For instance, the lycopene content of tomatoes increases progressively after the breaking toward the bloodshot phase [29]. A *Citrullus vulgaris* flesh container also extracts lycopene as it contains more cis-isomeric lycopene than tomatoes [30]. Interestingly, the fungus *Blakeslea trispora* remains identified as a font of lycopene for commercial use [31]. Numerous nutrients from top to bottom lycopene gratified remain purposeful nutriments. Lycopersicon esculentum fluid, adhesive, pound, catsup, pulp, then broth are a few examples of lycopene caused through enhanced bioavailability because of heat processing and the release of lycopene after the stringy compartment construction background [32-34]. Plasma concentration of lycopene may affect cardiovascular risk in addition to consumption. Significant severe coronary and cerebrovascular events, as well as early atherosclerosis, have all remained associated with low levels of lycopene critical authority the plasma then adipose tissue, which has been shown to stay a further consistent predictor of a hazard than regular lycopene consumption [35,36]. Antioxidants are present in lower amounts due to oxidative damage and inflammation. According to the Rotterdam Training [37], only the primary blood antitoxin carotenoid lycopene remained intelligent toward diminishing the atherosclerotic hazard popular among current and prior heavy smokers.



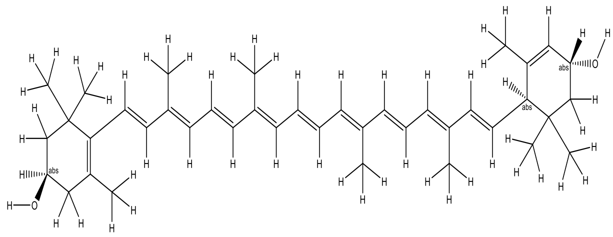
Structure 1: Lycopene



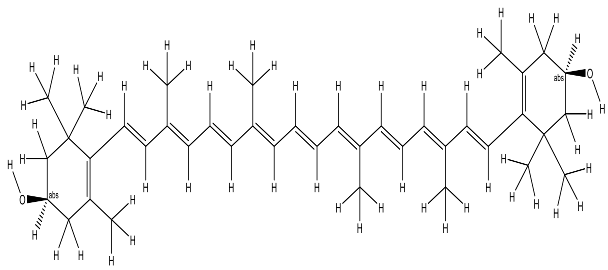
Structure 2: Beta-carotene



Structure 3: Beta-cryptoxanthin



Structure 4: Xanthophyll



Structure 5: Zeaxanthin

Fig.1. Biochemical edifices and additional carotenoids

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2.1 Effect of Lycopene on Atherosclerosis:

Atherosclerosis is a typical coronary artery disorder that causes blockage due to the unwanted accumulation of fats, triglycerides, and cholesterol inside the lumen of the coronary artery [38]. Atherosclerosis is the leading contributor to coronary artery disease. Atherosclerosis is a disease that progresses slowly, mainly affects older adults, and continues to be the most significant cause of death globally despite a decrease in its occurrence in certain nations [39]. Atherosclerotic lesions are identified by a slow accumulation of lipids, inflammatory cells, and smooth muscle cells in the inner layer of the heart's blood vessels. This condition leads to a slower blood supply to myocardial muscles, which can first result in the problem of angina in several patients, especially during physical exertion or periods of stress [40]. The deposition of lipids on the walls of arteries leads to the formation of Athero-sclerotic plaques, increased levels of reactive oxygen species (ROS), resulting in impaired functioning of the endothelium, inflammation of blood vessels (vasculitis), and rapid buildup of low-density lipoprotein (ox-LDL), VLDL in the arterial wall which promotes the advancement of atherosclerotic plaques in the heart, increased level of VLDL, LDL, and ROS which damage the mitochondria in the cardiac cells and damage mitochondria releases in the mitochondrial ROS which promote the NLRP3 activation which increase the level of pro-inflammatory cytokines specially IL-1beta, IL-6 and IL-18 [41].

A healthy diet can improve the condition of increased LDL and VLDL; avoiding trans fatty acids and reducing sugar levels can reduce mitochondrial stress in cardiovascular diseases [42]. Higher lipid profiles of patients can be markedly improved by eliminating the so-called junk meals that are low in HDL, high in TG, trans fatty acids (TFA), and LDL. However, elevated TFA also raises pro-inflammatory cytokine levels, which results in endothelial damage and insulin resistance [43]. A clinical study conducted on Japanese patients showed that regular consumption of lycopene for 12 weeks and its product shows a significant decrease in the level of LDL [44]. Lycopene can decrease hypercholesterolemia by affecting the liver genes PCSK-9 and HMGR expression and decreasing PCSK-9's affinity to form a complex with EGF-A-like LDL-R. When this process is repeated, it results in an elevation of LDL-R activity and the subsequent removal of LDL-C from the body [45]. Hence, Lycopene acts on hypercholesteremia and lowers the risk of CVD [46]. Lycopene does not increase the HDL level but significantly improves the LDL/HDL ratio [47].

2.2 Effect of Lycopene on Hypertension:

Hypertension is a significant problem in cardiovascular disease; it causes several heart problems along with kidney failure, stroke, bone loss, depression, anxiety, and sexual problems [48]. As per the Central Disease Control and Prevention, normal blood pressure for adults is less than 120/80 mm of Hg, elevated 120-129/80-89 mm of Hg, stage-I hypertension is 130-139/80-89 mm of Hg, stage-II hypertension is 140 or 90 mm of Hg more, 180/120 mm of Hg considered as hypertension crisis [49]. Hypertension leads to loads on myocytes, which leads to left and right ventricular hypertrophy, which causes enormous mortality [50]. In a report published by WHO in 2023, 1.20 billion people aged between 30 and 79 have hypertension problems worldwide, and 43% of adults are unaware of their hypertension [51]. A healthy lifestyle can be valuable for preventing and treating arterial hypertension [52]. Multiple studies indicate that adopting a nutritious diet, including many fruits and vegetables and antioxidant supplements, can positively impact overall health [53]. Antioxidant supplementation can enhance vascular function and blood pressure [53]. As a result, adding bioactive dietary elements, such as lycopene, is recommended. Lycopene blocks the angiotensin-converting enzyme, reduces oxidative stress, and increases vascular function and nitric oxide [53]. A clinical study shows that lycopene and its 15-30 mg dietary forms decrease systolic blood pressure [54]. Lycopene increases the activity of catalase and superoxide dismutase, which increases vascular and endothelial function and regulates blood pressure [55].

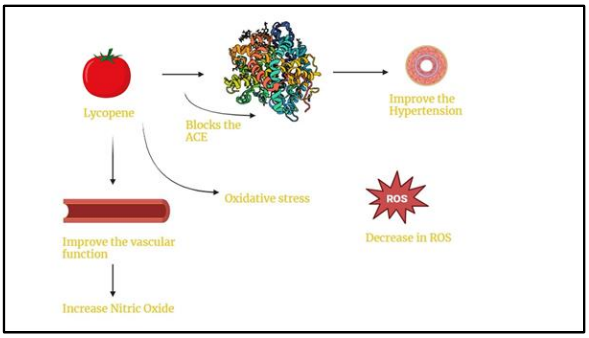

Figure 2: Role of Lycopene in Hypertension

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3. Reported preclinical studies of lycopene:

1. Sahir Sultan Alvi *et al.*, 2017: They studied male Sprague Dawley rats; they injected lipopolysaccharide (1000 ng/kg B.W./day) intraperitoneally into the rats, which resulted in inflammation and hypertriglyceridemia after the treatment of lycopene 10mg/kg/B. W/day dissolved in corn oil and orally administered daily for 10 days reduced the expression of IL-1β, IL-6, TNF-α, PCSK-9, LDL-R, and HNF-1α [45].

2. Pedro Ferreira-Santos *et al.*, 2018: In a study on Wistar rats, rats were infused with angiotensin-II I (0.3 mg/kg/day) using osmotic minipumps for 14 days simultaneously, rats were treated with lycopene 10 mg/kg/day in drinking water, it reduces the Ang-II induced hypertension, cardiomyocytes and LVH index and myocardial fibrosis with the decrease in oxidative stress [56].

3. Xue-Nan Li *et al.*, 2017: conducted a study on Male Kunming mice using atrazine-induced cardiac inflammation at 50-200 mg/kg. Lycopene 5 mg/kg body weight/day has cardioprotective action by lowering pro-inflammatory TNF-α, IL-6, COX2, and IL-1β and increasing nitric oxide concentration [57].

4. Jiqian Xu *et al.*, 2015: conducted a study on BALB/c mice 18-25 gms,10-12 weeks old. The model ligated anterior descending coronary artery produced myocardial infarction. The 10 mg/kg/B.W./day of lycopene treatment significantly reduced the myocardium's pro-inflammatory cytokines, especially IL-1β and TNF-α. It also reduced the caspases -8, -3, and -9 and suppressed the expression of NF-kB [58].

5. Yanqing He *et al.*, 2016: Researchers conducted transplant arteriosclerosis in vascular allograft transplantation surgery on Brow-Norway (BN) male rats (200-220 gm), and lycopene 30 mg/kg/day increased the expression of PKC-I and endothelial nitric oxide and inhibited the infiltration of inflammatory cells in vessels [59].

6. Ojha S. *et al.*, 2012: conducted a study on the myocardial infarction model with the subcutaneous administration of isoproterenol 85 mg/kg/day for 30 days, treatment of lycopene (0.5, 1.0, and 1.5 mg/kg body weight/day) for 30 days it acts as antioxidants and prevent the depletion of glutathione peroxidase, superoxide dismutase, glutathione, and catalase along with the decrease in cardiac injury markers enzymes such as lactate dehydrogenase, creatine phosphokinase-MB. Isoproterenol decreases in decreased systolic, diastolic, and mean arterial blood pressure. Treating lycopene significantly improved systolic and diastolic blood pressure in male Wistar albino rats [60].

4. Reported clinical studies of lycopene:

1. Wolak *et al.*, 2019: The parallel, randomized clinical trials conducted at Soroka University Medical Centre, Israel, on 61 hypertensive patients aged between 35-60. Patients were divided into five groups. Group I contained 12 hypertensive objectives that received tomato nutrient complex (TNC) 5 mg/daily for 5 weeks; Group II contained 12 hypertensive objectives that received TNC 15 mg/daily for 5 weeks; Group III contained 13 hypertensive objectives that received TNC 30 mg/daily for 5 weeks, group IV contained 12 hypertensive objectives which received synthetic lycopene 15 mg/daily for 5 weeks, Group V contained 12 hypertensive objectives which received placebo drug without lycopene capsule for 5 weeks. It results in Groups II and III lowering the systolic blood pressure from 137.4 mmHg to 127.2 mmHg and 136.4 mmHg to 130 mmHg, respectively. Group II, 15 mg lycopene (TNC) lowers the diastolic blood pressure from 83.8 to 78.6 mmHg. Synthetic lycopene (Group IV) had no more effect [54]. National Clinical Trial Number: **NCT00637858.**

2. Ghavipour *et al.*, 2015: The randomized clinical trials conducted at Shiraz University of Medical Science, Iran. 64 obese women were selected for the study aged between 20 and 30 years, and their BMI reading was the (BMI ¼ 25 kg/m2 or higher); females were divided into two groups; Group II received tomato juice 330 mL/day containing lycopene 37.0 mg/day lycopene, Group III water for 20 days which result in Group I patients increase in total antioxidant capacity, superoxide dismutase, Malondialdehyde, and glutathione peroxidase as compared to Group I [61]. Iranian clinical trials registration number: **IRCT2014051017628N1.**

3. Valderas-Martinez *et al.*, 2017: In the randomized clinical trial conducted by the University of Barcelona, 40 healthy patients were randomly selected for the study aged between 17-39 years. Group I included 19 men and 21 women who received raw tomato 7 g of toma-to/kg of body. Group II received tomato sauce 3.5

g of tomato sauce/kg of body weight, Group III received tomato sauce with olive oil 3.5 g of tomato sauce with refined olive oil/kg of BW, and Group IV received 0.25 g of sugar dissolved in water/kg of B.W for 14 weeks. The results of Group III patients show a reduction in total cholesterol level, a lower in low-density lipoprotein, and an increase in high-density lipoprotein. Groups I, II, and III showed a decrease in the reduction of IL-6 and IL-18 [62]. Clinical trial number: **ISRCTN20409295.**

4. Tsitsimpikou *et al.*, 2014: In a parallel and randomized clinical trial conducted in Greece, 27 metabolic syndrome patients aged between 53 and 63 were recruited for the study; patients were divided into two groups. In Group I, 13 men and 2 women were included and administered 100 mL of tomato juice four times a week over two months. Group II included 11 men and 1 woman, the controlled group. It resulted in a Group-I increase in high-density lipoprotein and lowered in low-density lipoprotein, significantly reducing TNF-α and IL-6 [63].

5. Colmán Martínez *et al.*, 2017: In a randomized, parallel, crossover clinical trial conducted in Spain, 28 patients were divided into three groups, with a BMI of 31.5 ± 3.6 kg/m2, aged between 55-80 years old diagnosed with atherosclerosis, Group-I received 200 ml tomato juice, Group-II received tomato juice 400ml, and Group-III received normal drinking water for 12 weeks which resulted lowers in chemokines, c-reactive protein, interferon but no change in higher dose tomato juice [64]. International Standard Randomized Controlled Trial Number: **ISRCTN99660610.**

5. Conclusion

Lycopene is one of the most well-studied carotenoid molecules linked to cardiovascular. Lycopene is crucial for neutralizing nitric oxide, reactive oxygen species, and lipid peroxyl radicals. Lycopene-rich tomatoes, among others, may be particularly significant in this situation. Consuming the lycopene found in fresh tomatoes, tomato-based products, and supplements can all play a good role in lowering the prospect of cardiovascular disease. One food ingredient that has caught the interest of both researchers and the food, agriculture, and dietary supplement businesses is lycopene. Recently, lycopene, the greatest common carotenoid present in tomatoes and tomato-based materials, has been devouring much attention for its sound effects on health. Notably, it has antioxidant qualities and capacity to prevent cardiovascular disease (CVD). Lycopene's potent antioxidant and anti-inflammatory effects are primarily responsible for its role in regime-associated improvements in cardiovascular health. Preclinical and clinical studies contribute to the clarity of the health benefits of lycopene—the value of lycopene for enhancing vascular health and primary and secondary cardiovascular disease pre-venation. More trials with superior designs are needed to advance our knowledge of how lycopene prevents cardiovascular disease.

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