

Lycopene: A Natural Antioxidant Carotenoids against Cardiovascular Diseases

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Abstract. Cardiovascular disease, as a common disease worldwide, is well known to the public because its risk factors are closely related to people's daily life and its prevalence is increasing year by year. At the same time, with the rise of supplements, lycopene has become an important ingredient in some supplements. Lycopene is contained in a series of edible plants and can also be obtained physically extraction or chemically synthesis. In recent years, the hypolipidemic and antioxidant effects of lycopene were confirmed, and scientists have illustrated some links between lycopene and cardiovascular disease. Although there have been studies on the physical benefits of lycopene in people, few articles have fully addressed the mechanisms by which lycopene prevents cardiovascular disease. Starting from the structure of lycopene and the etiology of cardiovascular diseases, this paper comprehensively analyzed the mechanism of lycopene preventing cardiovascular diseases in different ways. The food sources of lycopene are briefly explained in order to provide a clearer food choice for the population. The reasons for the differences in lycopene bioactivity and absorption were also mentioned. In order to scientifically explain the effect of lycopene supplementation on cardiovascular disease, differences were also shown before and after lycopene supplementation.

Keywords: Lycopene, Cardiovascular Diseases, Antioxidant, Supplement.

1. Introduction

With the aggravation of pressure in modern society, people's sleep and eating habits are becoming more and more irregular. Obesity, tobacco use, physical inactivity, and alcohol consumption-all these detrimental habits lead to an increasing trend in mortality of chronic diseases [1]. Cardiovascular disease (CVD) has been reported to be the main reason of death in the global population, and it continues to increase worldwide. The four leading causes of CVD are hyperlipidemia, blood hyperviscosity, atherosclerosis, and hypertension. Antioxidants found in nature are critical in preventing CVD. Many regions of the globe have benefited from natural antioxidants in tomatoes and some other plants with red color to prevent CVD for better human health. Nowadays, natural antioxidants' significance in boosting mankind's health has grown significantly in recent years by rapidly developing research on antioxidants. More and more natural ingredients are being used as dietary supplements to help people prevent chronic diseases, including CVD. According to recent studies, some phytochemicals not involved in metabolism from our daily diet may play a positive role in lowering CVD risk. Among them, lycopene has become a new favorite among many dietary supplements. Lycopene is a kind of lipophilic phytochemicals that can be extracted from tomatoes, tomato processed products, and some other red or orange vegetables and fruit [2]. In 1989, MASCIO found that lycopene had the best quenching activity against singlet oxygen in all kinds of carotenoids [3]. However, its amount and bioavailability vary dramatically in species and other factors [4]. Lycopene reduces CVD risk through its anti-inflammatory effect, low-density lipoprotein (LDL) lowering effects, and cholesterol concentration lowering effects, etc.[6-9]. Lycopene can also deeply

remove vascular waste, repair oxidized cells, promote intercellular glial formation, and enhance vascular flexibility [7]. This article will discuss its role in preventing cardiovascular disease from three aspects. Lycopene is also introduced as a dietary supplement.

2. Lycopene

Lycopene is a kind of phytochemical substance that was discovered by scientists in tomatoes and a few other red fruits. It is also a fat-soluble carotenoid. Among carotenoids common in vitro, it was been proved efficient in cleaning singlet oxygen and free radicals [3]. As a result, it serves as both a pigment and an antioxidant supplement in food preparation.

2.1. Sources

Lycopene can also be obtained from watermelons, pink grapefruit, psidium, guajave, pawpaw, and rosehip. In addition to being found in various vegetables and fruits, lycopene can also be obtained from chemical synthesis or physical extraction. For commercial production, lycopene has normally been attained by fermentation and isolation from natural sources. For example, it can be isolated from algae, fungi, plants and microbial organisms [8].

2.2. Chemical and Physical Properties of Lycopene

The structural formula of lycopene has been shown in Figure 1. Lycopene was found as open-chain polyisoprene with 40 carbon atoms and 11 conjugated double bonds. Its molecular weight is 536.88 Daltons [3]. Lycopene has a better absorption than α -carotene and β -carotene, and the cis form it is more easily absorbed than in the trans form.

Lycopene is inclined to aggregate in crystal form and immerse in an aqueous solution, and it is more easily dissolved in organic impregnant like chloroform and benzene. Secondly, the dissolvability of lycopene at room temperature is 0.2 g/L approximately in vegetable oil. In the ripe fruit, lycopene appears as a thin, needle-like crystal [9].

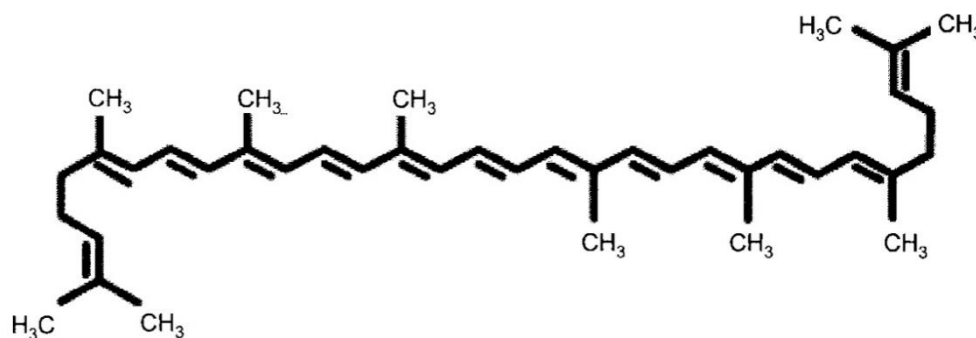


Figure 1. The structural formula of lycopene [3]

2.3. Lycopene and Vascular Health

From a dietary perspective, researchers have shown that eating tomatoes or other food containing lycopene can reduce the possibility to suffering cardiovascular disease that are chronic [1]. Lycopene has been proved with the properties of lipid lowering, reducing the LDL level, and promoting production of high-density lipoprotein (HDL).

The examined effects of lycopene related to cardiovascular health are mainly comprised of antioxidant and anti-inflammatory abilities. Lycopene also has the properties of antihypertensive, improves endothelial function, and reduces the risk of atherosclerosis [7]. Therefore, the scientists pointed out that lycopene has preventive and influential effects on cardiovascular disease. In recent years, more scientists have also been involved in the research and production of lycopene supplements.

3. Cardiovascular Diseases

Cardiovascular disease is a general term for ischemic or hemorrhagic diseases and usually occurs in the cardiac area, encephalon and tissues of the whole body. It usually means the presence of hyperlipaemia, high blood viscosity, arterial sclerosis, hypertension and other conditions. Cardiovascular disease is an acute menace to mankind's health, peculiarly a common disease in middle-aged and elderly people over 50 years old with great harm. Cardiovascular disease has been proved that the most widespread causation of death in the global. The survival of CVDs was poor and these diseases were increasing worldwide (Figure 2) [10]. Atherosclerosis accounted for over 50% of CVD. Lipid metabolism disorder is the pathological basis of atherosclerosis, macrophages in lesions promote inflammation and plaque formation and with the cholesterol sediment ceaselessly accumulate in macrophages in the large and medium-sized arteries, its progression may be clinically silenced for a period, then to the point where it directly led to severe consequence such as a heart attack or stroke [1].

3.1. Risk Factors of Cardiovascular Diseases

The increased incidence of cardiovascular disease may be due to a decrease in physical activity and the intake of energy-dense foods. Hypertension, low HDL and diabetes are also the risk factors for cardiovascular disease. Studies have shown that patients suffering with diabetes have 3 to 5 times possibility to get cardiovascular diseases than ordinary people [1]. Furthermore, several studies have related smoking to rates of cardiovascular disease, the likelihood of suffering CVD among people quitted smoking decreases approaches that of normal people in just 2 years.

Scientists point out that of all the risk factors, food nutrition can be effective with preventing or reducing heart health abnormalities. Phytochemicals like lycopene, along with other antioxidant nutrients found in fruits or some vegetables, can show vital influence in preventing disease.

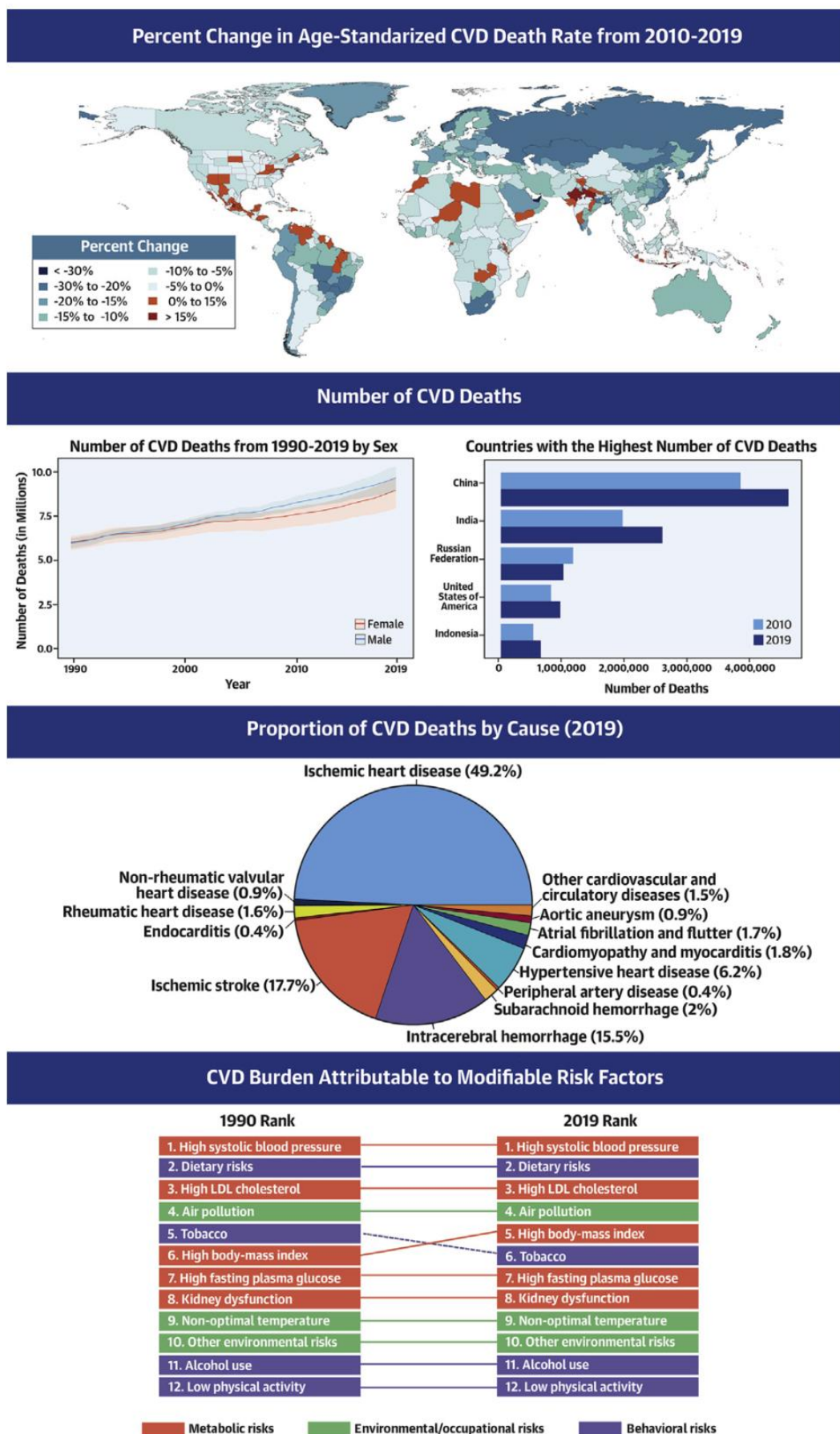


Figure 2. Global prevalence of cardiovascular disease and risk factors [10].

4. Mechanism of Lycopene in Reducing Cardiovascular Disease Risk

4.1. Anti-Inflammatory Effects

4.1.1 Inflammatory in The Process of Atherosclerosis

Inflammation is involved in the three stages of developing atherosclerosis: It is a disease in which the lipid forms in the arteries and eventually blocks the blood supply, which then causes the cardiovascular problem. As seen in Figure 3, Stage A is the single endothelial layer inflamed; adhesion molecules are produced, allowing leukocytes to attach, then the proinflammatory cytokines adhere the leukocytes to move into the intima. Stage B is when the single cytes turn into macrophages and engulf lipid particles; then become a feature of atherosclerotic plaques. T-lymphocytes join the macrophages, secrete growth and cytokines factors that increase the smooth muscle cell. In the stage C, T lymphocytes will further act, the production of smooth muscle collagen is inhibited, and the secretion of collagen-degrading enzymes is stimulated and increased. As a result, the ability to protect the blood from plaque thrombosis is impaired [11].

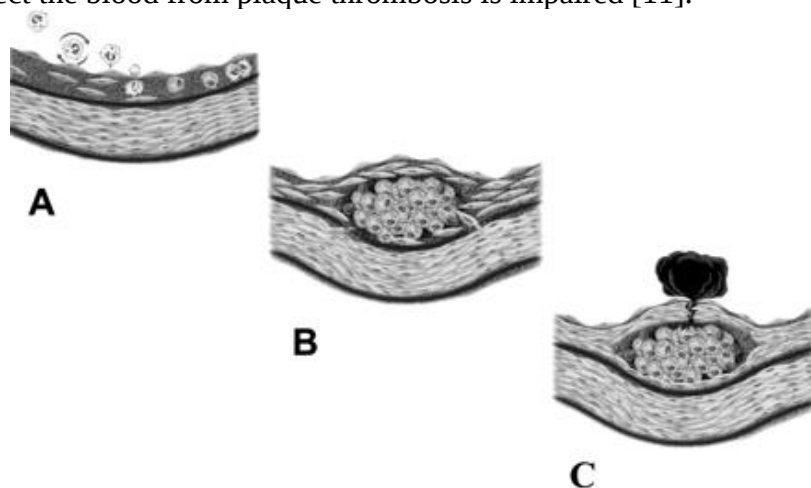


Figure 3. The participation of inflammation of three stages of atherosclerosis

4.1.2 Anti-inflammatory Effects of Lycopene

Lycopene's anti-inflammatory effects are associated with the many ways the molecule regulates cellular activity; it had very high hydrophobicity, which made its protection of cardiovascular more in the anti-inflammation part than the inhibition of oxidation [12]. It could inhibit pro-inflammatory cytokines produced in the body, which was a significant process of developing atherosclerosis [5]. It could protect the oxidative damage to cells and suppress the interaction between the monocyte-endothelium. From a study, lycopene was capable of improving the vasodilation mediated by the endothelial cells of people with cardiovascular disease, and the healthy patients control group didn't have any obvious effect observed; this result indicated that lycopene is capable in secondary prevention [13, 14].

4.2. Effects of Lycopene as an Antioxidant

Hypertension is the third common cause of cardiovascular disease and primary effect of renal failure and stroke. The existence of oxidative stress is a contributing element in hypertension's development. It lowered the nitric oxide (NO), leading to the change in blood vessel function and structure, leading to the consequences of vascular cell proliferation, migration, apoptosis, and endothelial dysfunction, which are all factors of hypertension [15]. Lycopene as an antioxidant is potent, it could reduce oxidative stress by indirectly enhancing nitric oxide (NO) synthesis and simply, it lowers blood pressure. From a six weeks lycopene supplements for moderate hypertension patients study, the result was significant; 100% of the patients who already using calcium channel blockers had a lower blood pressure than before, which showed the effect of lycopene's role in managing hypertension.

4.3. Reduction of LDL Oxidation

Oxidized LDL (ox-LDL) is a product of LDL oxidation. LDL oxidation has multiple consequences, which all are the factor that leads to cardiovascular disease, including the dysfunction of endothelial cell, vascular smooth muscle cells, macrophages, and the activation of platelet.

From a natural product antioxidant trial study, the increase of lycopene in the diet can increase the blood lycopene level by two times and can reduce the level of LDL oxidation and plasma lipid peroxidation. As a result, lycopene had the ability to mitigate coronary artery disease (CAD), which is a common cardiovascular disease in the United States [16]. Another study about natural product antioxidants showed that lycopene could reduce LDL oxidation from a high-fat diet and increase the rate of interleukin 6 (IL-6), which means lycopene could reduce the risk of cardiovascular disease (CVD). There were also some other LDL side factors that could reduce the risk of CAD, for example, enhanced LDL degradation [6]. It is essential to highlight the fact that not every study showed that lycopene can reduce LDL oxidation; it only worked in some specific situations [17].

4.4. Regulation of Cholesterol Concentration

Hypercholesterolemia, a key trigger to the development of atherosclerosis and other cardiovascular disorders, is caused by an imbalance in cholesterol levels. Cholesterol concentration can be increased either by high levels of LDLs in blood or the synthesis of cholesterol by cells themselves. In vitro studies showed that lycopene primarily lowered cholesterol levels concentration in two ways according to Figure 4.

4.4.1 The Activity of 3-hydroxy-3-methylglutaryl Coenzyme A (HMG-CoA) Reductase

Most cholesterol in the body derive from the cells themselves, and only a small part comes from food. HMG-CoA reductase stimulates the deacylation of HMG-CoA to mevalonate, which is an essential step in the synthesis of cholesterol in cells. HMG-CoA is the enzyme that controls the rate of cholesterol production. Lycopene inhibits this conversion by lowering HMG-CoA reductase expression and activity [18]. As this key reaction slows down, the rate of the synthesis of cholesterol will decrease.

4.4.2 Modulation of the Activity of LDL Receptors

Studies showed that lycopene-rich cells had uninhibited or even activated LDL receptor synthesis, which meant increased uptake of LDLs in serum by cells [19]. LDLs contain very high levels of cholesterol esters. If LDL can not be efficiently endocytosed into cells, it will oxidize and accumulate at blood vessel walls resulting in the attachment of plaque. The accumulation of plaque leads to the narrowing of blood vessels. If a large amount of plaque exist, it may have a tendency to develop atherosclerosis. This confirmed that lycopene can lower cholesterol levels by regulating the activity of LDL receptors.

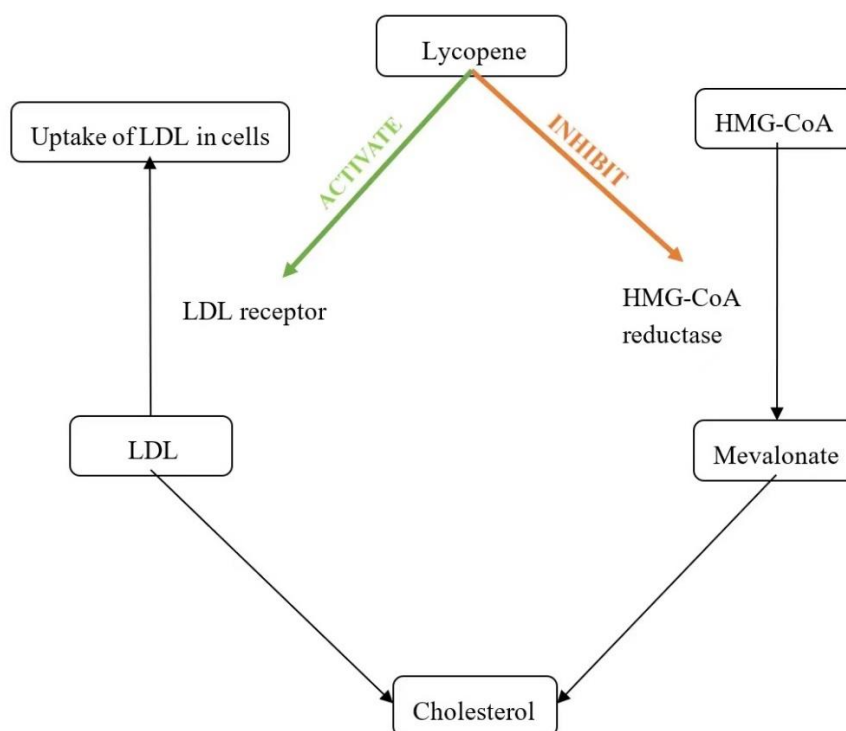


Figure 4. The mechanism of lycopene regulating cholesterol levels

5. Lycopene-rich Dietary Patterns

5.1. Food Sources

According to Figure 5, lycopene content varies dramatically by different types of food.

Many natural sources such as red and orange fruit vegetables contain lycopene. Tomatoes, papayas, grapes, peaches, apricots, melons, watermelons, and cranberries are significant natural sources of lycopene [2]. The growing environment such as temperature and soil quality can also affect lycopene levels. For example, tomatoes cultivated in the outdoors contain more lycopene than tomatoes grown in greenhouses [4].

Lycopene is abundant in a variety of processed tomato products, including tomato paste, tomato sauce, ketchup, and juices. Figure 5 has shown that the bioavailability of lycopene in processed products is more active. One of the reasons is that lycopene is a lipophilic carotenoid that increases its bioavailability when consumed with an oily substance [20]. Besides, lycopene bioavailability in tomatoes after thermal treatment is amplified compared to fresh tomatoes without processing [2].

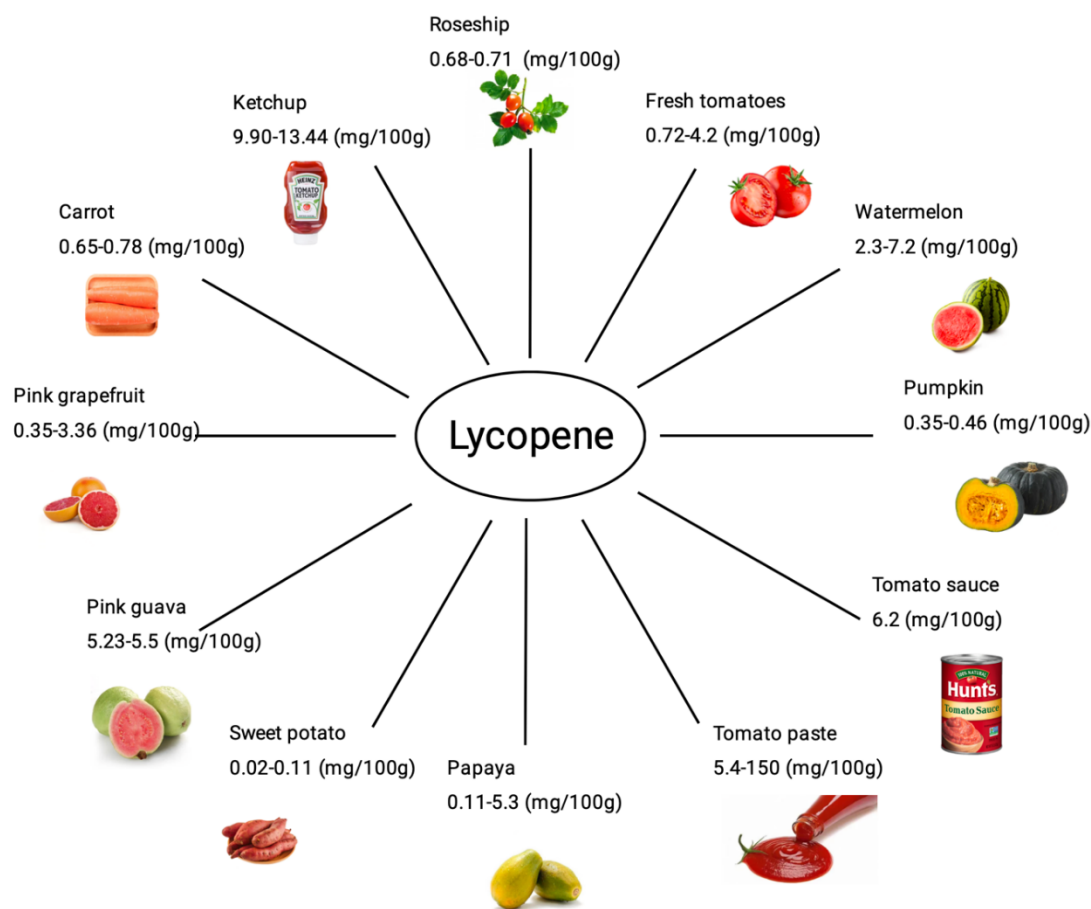


Figure 5. Lycopene content in different sources [21]

5.2. Intake Comparison Between Different Regions

Lycopene intake varies from region to region. The comparison of lycopene daily intake between different countries is shown in Figure 6. The daily intake of Spanish was the lowest compared to other European countries while the daily consumption in France, the UK, the Republic of Ireland, The Netherlands, and Belgium were similar, ranging from 4.1 mg/d to 5.01 mg/d. Adults in the U.S. consumed more than 7 mg/d lycopene every day.

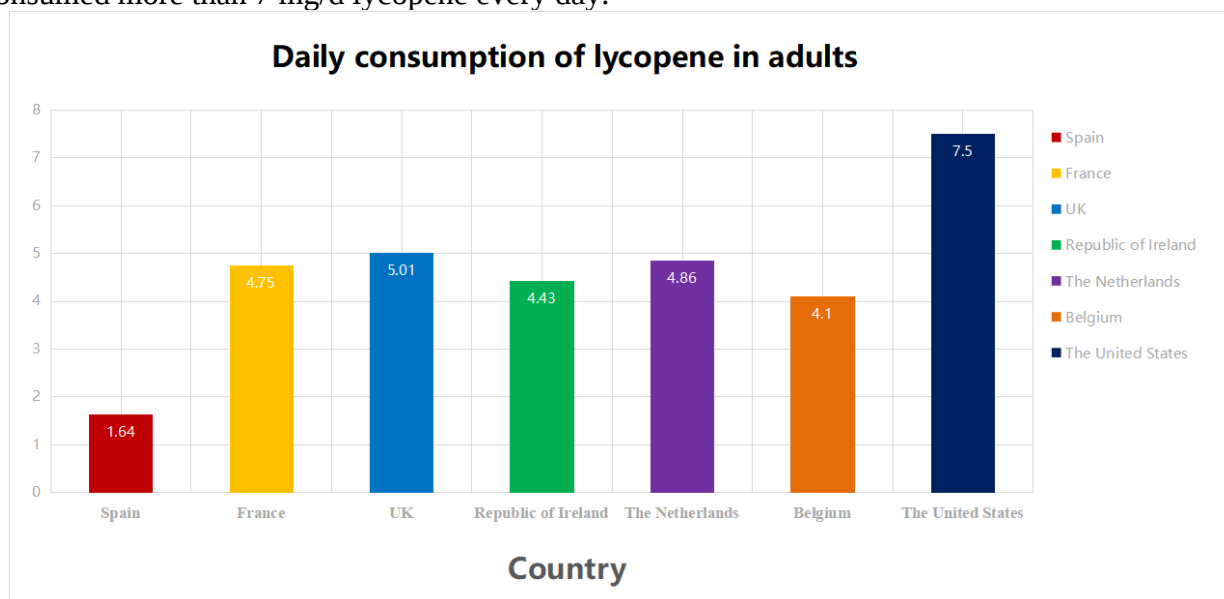


Figure 6. Comparison of lycopene intakes (mg/d) in adults in different countries [22-24]

5.3. Supplement of the Lycopene

Lycopene has the excellent antioxidant, anti-inflammatory properties and lycopene dietary supplement have been touted by the media for its property. As a result, a series of lycopene daily dietary supplements in the market to receive the favor of consumers. Unlike the natural lycopene in natural fruit and vegetables, the lycopene dietary supplement is synthetic crystalline lycopene. Lycopene supplements as a dietary supplement whose primary purpose is to maintain health especially help consumers against cardiovascular diseases. However, it's worth noting that regulation of these dietary supplements varies widely around the world. In the United States, for example, supplements like lycopene don't need to be marketed unless they claim to have medicinal benefits [2]. Therefore, it is necessary to discuss the effects of synthetic lycopene as a dietary supplement.

5.3.1 Differences Before and After Lycopene Intake

Consumers are often most concerned about the effectiveness of synthetic lycopene dietary supplements. However, according to a number of clinical trials, lycopene supplements do not seem to have a surprising impact on patients at risk of cardiovascular disease. Studies of lycopene dietary supplements over the past 20 years have found no clear evidence that increased lycopene supplement intake provides cardiovascular protection [25]. For example, Frank and his team did not find a significant effect of lycopene supplements in a group of randomized middle-aged people in 2012 [26].

The good news is that there are a number of clinical trials that proved the benefits of lycopene supplements for cardiovascular disease. For example, the 2006 Renu's trial demonstrated that lycopene dietary supplements were helpful in the short-term treatment of essential hypertension [27]. Systolic Blood Pressure and Diastolic Blood Pressure in these subjects were significantly reduced during lycopene capsules.

Most studies have not shown that lycopene as a dietary supplement can help consumers remit their cardiovascular disease, although it has shown some benefit in individual groups and diseases. After all, the evidence is still limited and there is no way to experimentally prove the efficacy of a single dietary supplement for a particular disease. Therefore, the effectiveness of lycopene as a supplement in the prevention of cardiovascular disease is still debatable.

5.3.2 Side-effects of Lycopene Supplement

According to various experiments, lycopene as a natural plant-based dietary supplement has not seen adverse side effects on humans. A previous study of lycopene synthesis in mice showed no sensory or motor abnormalities associated with lycopene. They also showed no signs of toxicity [28]. Base on the study, it is safe for consumers to take lycopene as a daily supplement.

6. Conclusion

Specific information related to lycopene and CVD along with the mechanism of lycopene in preventing CVD has been presented in this article. Lycopene can be found in a range of sources and can also be synthesized chemically or by other methods. Its lipid-lowering, antioxidant, anti-inflammatory and other effects have been pointed out that are related to preventing cardiovascular diseases.

Lycopene had a lot of effects on CVD. As an antioxidant, it not only has an anti-inflammation ability, but also can reduce LDL oxidation and regulate cholesterol concentration. Lycopene's anti-inflammation ability can inhibit the pro-inflammatory cytokine production and prevent cells from oxidative damage, which can reduce the inflammation involved in atherosclerosis. As an antioxidant, it can increase nitro oxide production, which helps reduce the risk of hypertension. And the reduction of LDL reduced the risk of CVD but only works in certain circumstances of people. In terms of its effect on cholesterol levels, lycopene can upregulate the expression of LDL receptors, or control cholesterol concentration by reducing HMG-CoA reductase activity. However, lycopene targets endogenous synthetic cholesterol and has limited effectiveness in limiting dietary cholesterol intake.

Currently, lycopene supplements are less commonly used to prevent cardiovascular disease compared to some polyunsaturated fatty acids. The lycopene dietary supplements have not been found to be significantly linked with the prevention of CVD in most studies. Only a few studies did show the lycopene dietary supplement helped for people who have CVD or underlying CVD. After all, it's a dietary supplement not a drug. It is undeniable that lycopene, as a natural dietary supplement, has a bright prospect in the prevention of CVD in the long run. In the future, lycopene is likely to be more widely used because its ingredients are more readily available and cheaper. What we need to pay attention to is that the absorption of lycopene depends on many factors, including your current health level, genetics of absorbing lycopene, your diet plan, etc.

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