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Review

Can lycopene be considered an effective protection against cardiovascular disease?

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ABSTRACT

Lycopene is a bioactive component mainly found in tomato. It is characterized by a high antioxidant potential, the highest among carotenoids. Mainly due to this property, lycopene has been suggested to display many beneficial effects, including its potential cardioprotective role. Despite some contradictory observations, which appear to be mainly caused by discrepancies in the different experimental protocols applied in the different studies, growing evidence points to clear benefits of lycopene in the maintenance of cardiovascular function and health. The knowledge about lycopene's preventive effects in atherosclerosis, and other cardiovascular diseases, must be translated into changes in food patterns, aiming to increase the consumption of tomato, tomato-containing products, or other foods with high lycopene content, which can have an important impact on cardiovascular disease, particularly in countries where this represents a major public health concern.

1. Introduction

Unhealthy food ingestion is a major cause of numerous pathologies, among which are cardiovascular diseases. This group of diseases, which represent the leading cause of death and incapacity worldwide are mainly caused by dysregulated plasma lipid levels, pro-inflammatory status and excessive production of reactive oxygen species (Gonzalez & Selwyn, 2003). In this context, there are many molecules, some of them not required for human biochemistry and metabolism, which may confer cardioprotection and lower the risk of cardiovascular disease. Among them, antioxidants appear to have a high potential and have been implicated in such protection (Petyaev, 2016).

Lycopene belongs to the family of the lipid-soluble antioxidants called carotenoids, which are present in fruits and vegetables (El-Agamey et al., 2004; Tapiero, Townsend, & Tew, 2004). Although lycopene can be found in many other fruits and vegetables, it is mainly found in tomatoes, or tomato-containing products, which account for about 80% of total lycopene ingestion (Bohm, 2012; Moran, Erdman, & Clinton, 2013). Besides being the carotenoid with the highest antioxidant potential, lycopene has also the ability to modulate several key events that are important in the context of cardiovascular diseases, such as inflammation, apoptosis or cellular communication (Thies, Mills, Moir, & Masson, 2017). The main disadvantage of lycopene is related to its low bioavailability, which depends not only on the different lycopene biochemical isoforms, but also on the context of ingestion and on the genetics of each individual (Borel, Desmarchelier, Nowicki, & Bott, 2015; Petyaev, 2016; Zubair et al., 2015). The sum of these variables may account for some of the contradictory information regarding the real effects of lycopene in cardiovascular disease protection. Nevertheless, growing evidence points to robust benefits of lycopene intake, which will be discussed in the present review.

2. Biochemical properties of lycopene

Carotenoids are coloured lipid molecules mainly found in vegetable products, such as fruits, leaves, tubers or roots (El-Agamey et al., 2004; Tapiero et al., 2004). They can be divided into three groups, namely, carotenes, xanthophylls and lycopene (Jomova & Valko, 2013; Rutz, Borges, Zambiazi, da Rosa, & da Silva, 2016). Globally they present antioxidant properties, and although only a few are indispensable for humans, they are considered very important dietary bioactive components. There are more than 700 different carotenoids found in nature, but only six of them are found in significant amounts in human serum, namely, α-carotene, β-carotene (Fig. 1), β-cryptoxanthin, zeaxanthin, lutein and lycopene (Maiani et al., 2009). Biochemically they are isoprenoid compounds with a tetraterpene structure (Kaulmann & Bohn,

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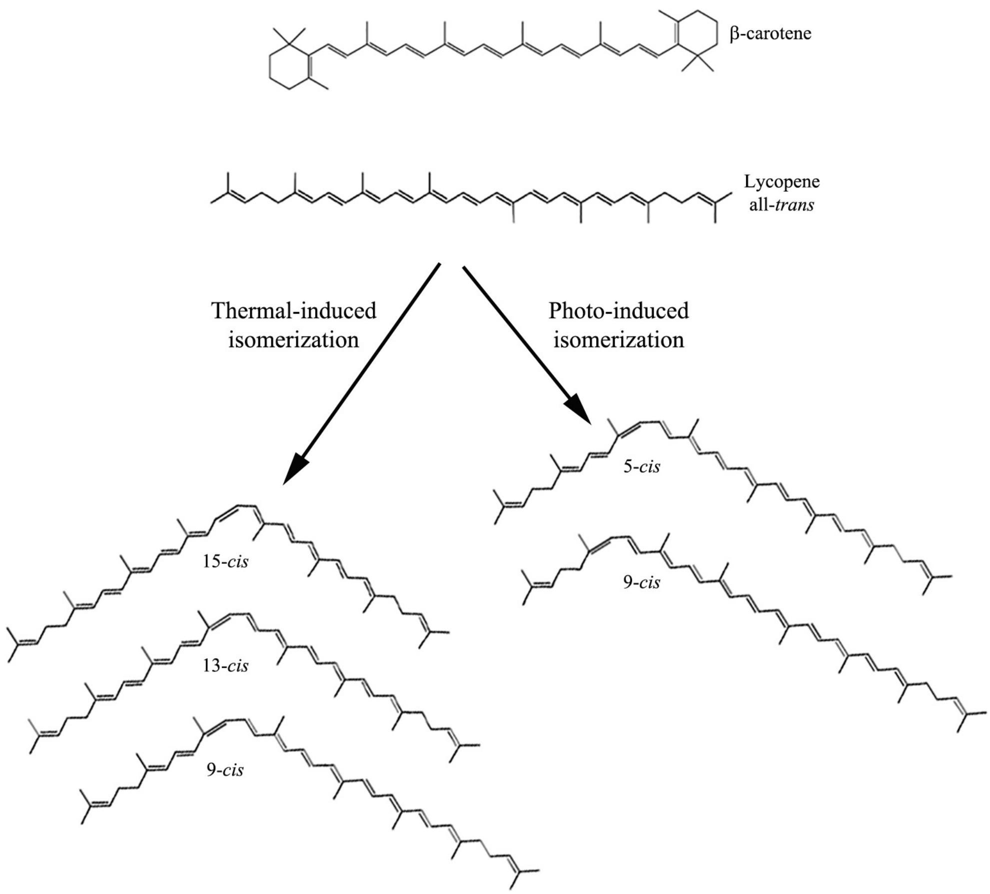

Fig. 1. Chemical structure of β-carotene, lycopene and its isomers obtained by thermal processing and light exposure.

2014). The majority present a central carbon chain with conjugated double bonds and various cyclic or acyclic groups (Stahl & Sies, 2005).

Although it was originally isolated from black bryony, lycopene is particularly abundant in tomato (Milani, Basirnejad, Shahbazi, & Bolhassani, 2016), but it is also found in several other food resources, such as pepper, papaya, watermelon, carrots, pink guava and grapefruit (Assis et al., 2017; Milani et al., 2016). It is a lipophilic molecule with 13 double bonds, which include 11 that are conjugated (Fig. 1) (Petyaev, 2016). In nature, all the double bonds are found in the *trans* configuration (Jackson, Braun, & Ernst, 2008). Exposure to light, digestion and thermal processing of lycopene promotes *trans*-to-*cis* isomerization (Fig. 1) (Moise, Al-Babili, & Wurtzel, 2014). This transition is believed to be important to increase the efficiency of its intestinal absorption, a process thought to be mediated by SR-BI but not NPC1L1 membrane transporter (Moussa et al., 2008; Schweiggert et al., 2014). Lycopene's open-polyene chain, without the ionone ring found in β-carotene, confers this molecule with a very high antioxidant capacity, which is significantly higher than that of other carotenoids, namely, more than twice that of β-carotene and about 10 times higher than that of α-tocopherol (Engelmann, Clinton, & Erdman, 2011; Milani et al., 2016). It is particularly effective in the quenching of superoxide anion free radicals, although the cis-isoforms are also very effective against peroxyl radicals (Engelmann et al., 2011; Jackson et al., 2008). Although the antioxidant properties of lycopene are well-known, the exact mechanism of action remains to be elucidated (Zhang, Liu, & Lv, 2016). Serum levels are strongly dependent on the intake of tomato products (Allen et al., 2003; Ganji & Kafai, 2005), and it is the most abundant carotenoid found in serum in Americans and the second in Europeans (Erdman, Ford, & Lindshield, 2009; Jenab et al., 2005).

Its half-life in humans also depends on the configuration of the conjugated double bonds, being 5.3 and 8.8 days for all-trans and all-cis isomers, respectively (Moran et al., 2015). One of the main obstacles, when considering the biological effects of lycopene, is its very low and variable bioavailability, which depends on the combination of at least twenty-eight single nucleotide polymorphisms (Borel et al., 2015; Zubair et al., 2015). Other factors accounting for this situation include the configuration of the double bonds, the geographic location of individuals, other sociodemographic factors, health status and, obviously, the food ingestion context (Petyaev, 2016). This high complexity may account, at least partially, for the elevated inter-individual variability of lycopene concentrations and biological effects. Moreover, lycopene distribution throughout the human body is asymmetrical, being mostly found in liver, adrenals, lungs, prostate and skin (Moran, Clinton, & Erdman, 2013).

Plasma levels of lycopene are very different among different populations and may reflect not only the endogenous properties of each individual, but, as previously mentioned, the diet. Globally, Northern and Western Europe along with America seem to be the regions with the lower ingestion of lycopene, while Asia and Central Africa appears as the region with the highest values (Murphy, Barraj, Spungen, Herman, & Randolph, 2014). The main dietary source of lycopene, worldwide, is tomato (a significantly higher intake than carrots); however, in Asia, lycopene comes mainly from watermelon (~50%), but also from tomatoes (~30%). Regarding the high plasma levels of lycopene found in Asia, it is important to highlight that that region is becoming one of the largest worldwide tomato producers, which may account for the observed plasma levels. Furthermore, it is estimated that tomato consumption accounts for 10–20% of the total vegetal consumption in the Pacific region of Asia. Also, metabolic relationships on the bioavailability and utilization of lycopene, as well as lifestyle, may contribute to the observations highlighted before, significantly accounting for the differences observed in lycopene plasma values among the world.

Lycopene has the potential to modulate many different cellular processes. There are multiple forms by which it can act in target cells

(Feitelson et al., 2015; Friedman, 2013; Thies et al., 2017). It was observed that lycopene can promote apoptosis and inhibit cell proliferation both *in vitro* and *in vivo* (Gupta, Bansal, & Koul, 2013; Uppala, Dissmore, Lau, Andacht, & Rajaram, 2013). Also, it is able to stimulate cell differentiation *in vitro*, particularly due to a positive effect in gap junction communication (Stahl, von Laar, Martin, Emmerich, & Sies, 2000). Other important mechanisms of action of lycopene include the inhibition of angiogenesis and oxidative damage, and the stimulation of phase II enzymes expression and activity, both *in vitro* and *in vivo* (Chen, Lin, Yang, & Hu, 2012; Lian & Wang, 2008; Palozza, Simone, Catalano, Russo, & Bohm, 2012). Also, as discussed below, lycopene have the ability to modulate inflammation, which may account for its health potential benefits.

Since oxidative stress has been linked to numerous pathological conditions, carotenoid ingestion, and, particularly, lycopene consumption, is associated to a decrease in the risk of chronic conditions such as inflammatory disorders, cancer, gastrointestinal, cardiovascular and neurodegenerative diseases, as well as to an increase in the immune system function (Ghavipour et al., 2013; Lorenz et al., 2012; Milani et al., 2016). Nevertheless, as highlighted in the present review, the mechanisms of action of lycopene lay far beyond its antioxidant properties and, thus, the potential effects of lycopene on human cells are multiple.

3. Pathophysiology of cardiovascular disease

Cardiovascular diseases are the main cause of mortality and morbidity around the world. They present a complex pathogenesis, the majority of them being caused by ischemic events and, globally, they can be considered as the result of a sum of different complementary factors, such as increased blood lipid levels and blood pressure, as well as endothelial dysfunction (Gonzalez & Selwyn, 2003). Although nowadays there are numerous technical interventions that can be conducted in order to treat patients, such as coronary bypass surgery, thrombolysis, or angioplasty (Tong et al., 2016), special attention must be taken regarding primary prevention, since this group of diseases is mainly caused by modifiable risk factors. Among them, perhaps the most important one is diet. It is well-known that Mediterranean countries have a lower rate of cardiovascular disease mortality (Garcia-Fernandez, Rico-Cabanas, Rosgaard, Estruch, & Bach-Faig, 2014), which is at least partially attributable to the healthy eating lifestyle. The so-called Mediterranean diet is based on the ingestion of high amounts of fresh fruit and vegetables, with one of the most ingested being the tomato (Petyaev, 2016).

In the context of cardiovascular ischemic diseases, it is also important to considerer that reperfusion after prolonged ischemia may lead to myocardial injury, which, in turn, can cause infarct expansion and/or arrhythmias (Tong et al., 2016). However, either in the case of the initial lesion, or in the case of reperfusion lesions, oxidative stress appears to have a central role (Tong et al., 2016). Thus, high antioxidant levels, including those of lycopene, may contribute in preventing or, at least, decreasing, the extent of these lesions.

Cardiovascular diseases have a complex pathophysiology, with several parameters critical for their development and, consequently, for the clinical outcome. The main parameters are summarized in Table 1. One key event in the development of the vast majority of cardiovascular diseases is the oxidation of low density lipoprotein (LDL) (Aviram, 1993; Steinberg & Witztum, 2010). Its accumulation in the sub-endothelial space, and further recognition by the scavenger receptors found on the surface of macrophages, causes the formation of foam cells, which are characteristic of the atherosclerotic lesions. Besides this important role in the pathogenesis of atherosclerosis, oxidized LDL also promotes endothelial dysfunction, increases the production of superoxide anion radical and the remodeling of the smooth muscle layers on vascular walls (Galle, Hansen-Hagge, Wanner, & Seibold, 2006). In this context, the high antioxidant potential of lycopene may account for a decrease in LDL oxidation and, thus, decrease the risk of cardiovascular disease. For the other two parameters (blood pressure and flow-mediated dilation), the action of NO as a key vasodilator appears to be strongly dependent on the redox status of the cellular environment, since the endothelial-derived free radicals may neutralize it. So, lycopene, as well as other antioxidants, may have an important role in the prevention of excessive NO neutralization and, consequently, in the maintenance of a proper vessel diameter. Taken together, there are numerous factors involved in the genesis and development of cardiovascular diseases, and the majority of them seem to have the potential for being modulated by bioactive compounds, including lycopene.

4. Cardioprotective properties of lycopene

4.1. Controversies

Due to the complex nature of cardiovascular disease, many dietary phytochemical properties have been suggested to play an important role in cardiovascular protection. For example, the consumption of nitrate-rich food, due to its potential to increase NO plasma levels, has been linked to improvements in endothelial integrity and function (Lara et al., 2016) and also to a decrease in blood pressure (Siervo, Lara, Ogbonmwan, & Mathers, 2013). Also, dietary antioxidants, such as carotenoids, appear to be potential key players in the prevention of cardiac and vessels pathologies (Mozaffarian, Appel, & Van Horn, 2011). In line with this, in a meta-analysis of sixteen cohort studies, involving more than 800,000 subjects, it was observed that the mortality associated with cardiovascular disease is lowered by a higher consumption of fruit and vegetables, namely, up to five servings/day (Wang et al., 2014). This effect appeared to be sensitive to the number of servings.

Since among carotenoids, lycopene is the one with the highest antioxidant potential, generally it has been linked to a decrease in cardiovascular disease risk (Jacques, Lyass, Massaro, Vasan, & D'Agostino, 2013; Sesso, Liu, Gaziano, & Buring, 2003; Yeo, Kim, Lim, Kim, & Lee, 2011). Although theoretically this relationship is consistent with the knowledge of the impact of oxidative stress in cardiovascular disease, and there is growing evidence that points that way (Table 2), in practice it remains, at least in some aspects, controversial.

Although the majority of the studies are favourable to positive effects of lycopene on cardiovascular health, there are also several studies that have failed to prove a consistent relationship between lycopene intake and a decreased risk of cardiovascular disease markers or outcome (Li & Xu, 2014; Osganian et al., 2003; Sesso et al., 2003; Tavani,

Table 1
Impact of different cardiovascular parameters on cardiovascular disease.

Cardiovascular parameter	Normal healthy levels	Cardiovascular disease outcome
LDL levels[a)]	< 2.6 mM	Reduction of 1 mM elicits a decrease of 23% in the risk of occurrence of myocardial infarction and 12% in all-cause mortality
Blood pressure[b)]	< 120/80 mmHg	Reduction of 5 mmHg cause a decline in cardiovascular disease mortality of about 9%, with a decrease of 13–14% in the case of stroke
Flow-mediated dilation[c)]	7–10%	Increase of 1% causes a reduction of 10–13% in the risk of cardiovascular pathological events

a) Baigent et al., 2005/b) Chobanian et al., 2003; Reboldi et al., 2011/c) Matsuzawa, Kwon, Lennon, Lerman, & Lerman, 2015; Xu et al., 2014.

Table 2
Main cardiovascular protective effects of lycopene.

Effects	Reference
↓ ischemic heart disease	- Riccioni et al., 2009
↓ coronary insufficiency	- Wolak & Paran, 2013
↑ HDL functionality	- Thies et al., 2012
↓ plasma LDL-cholesterol levels	- Cheng et al., 2017
↑ endothelial function	
↓ risk of cardiovascular disease	- Song et al., 2017
↓ arterial thickness	- Karppi et al., 2013
↓ risk of atherosclerosis and/or stroke	
↑ protection of endothelial cells from oxidative damage	- Hung et al., 2008
↓ monocyte-endothelium interactions	- Sawardekar et al., 2016
↓ platelet aggregation	
↓ oxidative response of neutrophils	- Marcotorchino et al., 2012
↓ secretion of pro-inflammatory cytokines	- Zou et al., 2013
↓ proliferation of smooth muscle cells	- Lo et al., 2007
↓ activation of monocytes and T-lymphocytes	- Mills et al., 2012
↓ C-reactive protein levels in women	- Biddle et al., 2015
↑ vasodilation mediated by endothelial cells	- Gajendragadkar et al., 2014

Gallus, Negri, Parpinel, & La Vecchia, 2006; Thies et al., 2017). These include human intervention studies, prospective studies, and retrospective studies. There might be many different reasons underlying these negative associations. As stated above, lycopene bioavailability and metabolism is strongly influenced by genetic variability, being described at least 28 single nucleotide polymorphisms in 16 genes, among which are those coding for the cholesterol membrane transporter scavenger receptor class B, member 1 (SCARB1), the molecular guidance cue slit homolog 3 gene (SLIT3) and the steroid-breakdown enzyme dehydrogenase/reductase (SDR family) member 2 (DHRS2) (Borel et al., 2015; Zubair et al., 2015) and, thus, results would be significantly influenced by this issue. Also, the cardiovascular markers used in the different studies varied significantly (ranging from biochemical parameters such as LDL levels or blood pressure, to clinical outcomes like occurrence of myocardial infarction, stroke or death) which makes detailed comparisons among them difficult. The variability found in the lycopene sources (ranging from fresh tomatoes to processed tomatoes, tomato-containing foods or even lycopene supplements), lycopene doses, ingestion of foods containing other compounds that may potentiate or decrease lycopene effects and duration of the experiments, may also account for some of the observed discrepancies. Furthermore, many published works used less than 100 volunteers, which decreases their statistical power and, thus, caution is required in the interpretation and extrapolation of the results. Knowing in advance that there are no perfect experimental protocols, it is recommended that future retrospective experiments should be conducted with large populations (preferably from the same geographic location, in order to avoid a high genetic variability), if possible framed in cohorts well-characterized from a food pattern point of view. At the same time, prospective studies, in which the amount and processing of tomatoes ingested are strictly controlled, may be informative at the level of possible biochemical alterations that decrease or increase the risk of developing cardiovascular disease. In this case, special attention must be paid to the experimental period, since lycopene ingested prior to the start of the study may persist in the body for a significant time. Thus, a period of washout of lycopene from previous ingestion is recommended.

4.2. Lycopene and cardiovascular risk factors

Recently, the impact of lycopene supplementation in cardiovascular disease risk factors was reviewed (Burton-Freeman & Sesso, 2014). Once again, the different experimental protocols found in the different studies caused difficulties in the comparison of results, but it appeared that the consumption of lycopene-containing food may be more effective than the use of lycopene supplements. This is probably due to the presence of other important compounds in tomato products, such as bioactive molecules and also electrolytes, that may potentiate the lycopene bioavailability and the lycopene-related effects (Friedman, 2013). In another recent study, an inverse association was observed between lycopene consumption and the incidence of ischemic heart disease, as well as coronary insufficiency, which is in line with the previous findings (Riccioni et al., 2009; Wolak & Paran, 2013).

In a randomized trial performed with 225 volunteers, the authors were unable to demonstrate significant effects of lycopene consumption, from tomato-containing food, on conventional inflammatory, vascular and lipid markers. However, lycopene elicited an improvement in high density lipoprotein (HDL) functionality (Thies et al., 2012).

4.3. Lycopene and cardiovascular function

Recently, a systematic review and meta-analysis was conducted, concerned with the effects of lycopene and cardiovascular function (Cheng et al., 2017). Only interventional studies with human subjects with dietary exposure to tomato-based products or lycopene supplements were considered, giving a total of twenty-two publications. Globally, it was observed that not only did lycopene appear to elicit a decrease in plasma LDL-cholesterol levels, but also an increase in endothelial function. Regarding the former effect, it is important to highlight that once again, only lycopene-containing foods, but not lycopene supplements, were able to promote it. Furthermore, a decrease in blood pressure (both systolic and diastolic), triglycerides, inflammation and adhesion markers, as well as an increase in HDL-cholesterol, also seemed to be linked to a high ingestion of lycopene-containing food/supplements, although in this case, the evidence was not so robust (Cheng et al., 2017). These results are in line with previous meta-analysis studies in this area (Li & Xu, 2013; Ried & Fakler, 2011). Interestingly, important differences among different countries were also highlighted, which suggests that the geographic context and culture may also modulate the cardioprotective effects of lycopene (Cheng et al., 2017; Li & Xu, 2013; Ried & Fakler, 2011).

In a recent meta-analysis study, aiming to evaluate the relationship between lycopene intake, its plasma levels and cardiovascular disease, it was observed that lycopene was associated with a 17% reduction in the risk of cardiovascular disease, when comparing the highest analyzed intake with the lowest one (Song et al., 2017), The reduction of cholesterol levels and inflammatory response, the decreased oxidation of biomolecules, the improvement of intercellular communications and stimulation of apoptosis and the antiangiogenic effects were among the proposed mechanisms involved in lycopene's cardiovascular protective effects. The effects on cholesterol levels may be attributable to different actions, like inhibition of cholesterol synthesis and modulation of LDL receptor and intracellular storage of cholesterol (Palozza, Catalano, Simone, Mele, & Cittadini, 2012).

4.4. Lycopene and inflammation

The anti-inflammatory effects of lycopene have been linked to numerous ways in which this molecule can modulate cellular activities. High lycopene levels seemed to be inversely related with arterial thickness and, putatively, with the risk of atherosclerosis and/or stroke (Karppi, Kurl, Ronkainen, Kauhanen, & Laukkanen, 2013). Also, it can directly protect endothelial cells from oxidative damage, and inhibit monocyte-endothelium interactions, as well as platelet aggregation (Hung et al., 2008; Sawardekar, Patel, & Uchil, 2016). Furthermore, lycopene may suppress the oxidative response of neutrophils, as well as the secretion of pro-inflammatory cytokines (Marcotorchino et al., 2012; Zou, Feng, Ling, & Duan, 2013). The proliferation of smooth muscle cells, as well as monocytes and T-lymphocytes, also appear to be downregulated by lycopene (Lo et al., 2007; Mills, Wilson, & Thies, 2012).

In a study conducted with heart failure patients, lycopene consumption promoted a decrease in C-reactive protein levels in women, but had no significant effect in men (Biddle et al., 2015). In another study, lycopene supplementation was able to improve vasodilation mediated by endothelial cells, in cardiovascular disease patients, while in the healthy control patients, no significant effect was observed (Gajendragadkar et al., 2014), suggesting that lycopene may be particularly effective as a secondary prevention player.

Thus, although lycopene presents a very high antioxidant activity, at least in some cases its role in cardiovascular protection appears to be more related to its anti-inflammatory properties, than to the inhibition of the oxidation of LDL, since lycopene, due to its elevated hydrophobicity, is more likely to be found in the nuclear hydrophobic core of the lipoprotein (Muller, Caris-Veyrat, Lowe, & Bohm, 2016). Nevertheless, it was proposed that the consumption of one or more servings/day of tomato-rich products is related to a lower risk (30%) of cardiovascular disease (Sesso et al., 2003). Quantitatively, the cardioprotective effects of lycopene seemed to be relevant following 1–180 days of tomato-products ingestion (70–400 g/day) (Cheng et al., 2017). For comparison, the average consumption of lycopene ranges between 5 and 7 mg/day in the developed countries, which corresponds to ~50 g of tomato-products (Wang, 2012).

It is important to note that the conflicting results about the potential cardioprotection elicited by lycopene may be related to the wide variety of experimental protocols used to discover any association between lycopene consumption and cardiovascular disease. These important differences include the pre-existing levels of lycopene, the source of lycopene (tomato products, supplements, etc.), the characteristics of the target populations (healthy, unhealthy, smokers, non-smokers, etc.), the amount of lycopene consumed, the duration of lycopene supplementation and the analyzed markers/cellular effects. Interestingly, and despite all the observed differences, it was proposed that total carotenoid levels may predict all-cause mortality and poor outcomes and rapid progression of cardiovascular disease (Shardell et al., 2011). Although, globally, carotenoids are not indispensable micronutrients, they have very important biochemical features that make them useful allies in promoting a good health status.

5. Conclusion

Despite some controversy about specific effects of lycopene in cardiovascular protection, growing evidence points to unequivocal benefits of lycopene intake both in terms of cardiac, endothelial and vascular function and health. The underlying mechanisms by which lycopene exerts its effects are now being unravelled, and might explain some of the contradictions observed in the literature. The genetic inter-individual differences may also be a key issue in understanding the real effects of lycopene in each individual. The context of ingestion of lycopene also appears to be important, since globally the beneficial effects were more significant for the ingestion of food-containing lycopene (particularly tomato products), than for lycopene supplements. Thus, the ingestion of lycopene-containing food, may be relevant for the prevention of atherosclerosis and other cardiovascular diseases and, consequently, must be considered an important strategy, particularly in countries where these diseases are a major public health concern. Also, conditions that promote long-lasting oxidative stress, such as physical exercise, smoking or chronic pathologies, may cause a significant decrease in lycopene levels, and, thus, an efficient replenishment of that molecule may be required. Taken together, recommendations for lycopene intake must take into account not only its low bioavailability and asymmetrical distribution throughout the human body, but also the conditions that can accelerate the loss of lycopene. So, the establishment of individualized nutritional approaches and recommendations that consider all of these factors may have a profound impact on cardiovascular disease and, consequently, on human health.

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