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Pleiotropic role of lycopene in protecting various risk factors mediated atherosclerosis

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Abstract

Lycopene, a carotenoid which is commonly present in vegetable products and fruits, is one of the most effective antioxidants among dietary carotenoids. Dietary ingestion of lycopene has been shown to be inversely associated with risk of chronic diseases, such as cardiovascular diseases (CVDs) and cancer that could be due to its antioxidant potential. Since, a number of risk factors like hypercholesterolemia, smoking, infection/inflammation, *etc*. are involved in atherosclerosis progression and current remedial strategies are directed towards long term use of chemically synthesized drugs that leads to host of side effects, so a solo safer agent with pleiotropic property is still warranted. Current review summarizes the role of lycopene in risk factors mediated progression of atherosclerotic process on the basis of different *in vitro* and *in vivo* experimental evidences in order to explore new possible multiple therapeutic action of lycopene.

Key words: Lycopene, atherosclerosis, HMG-CoA reductase, inflammation, LDL, HDL

1. Introduction

Cardiovascular diseases (CVDs) have been reckoned amongst the top reasons for early deaths in the world. In 2002, CVDs contributed to approximately one third of entire global deaths, whereas, by the year 2020, it is expected that CVDs will become the leading cause of death and disability worldwide (Ginghina *et al.*, 2011). Therefore, CVD has become an increasing burden to the global economy and a major causative factor for development of CVD and atherosclerosis. There are number of risk factors which induce the progression of atherosclerosis such as hypercholesterolemia, cholesterol induced oxidative stress, elevated levels of low density lipoprotein (LDL) cholesterol, hypertension, tobacco use, cigarette smoking and diabetes. Several epidemiological studies have identified LDL and high density lipoproteins (HDL) as independent risk factors that modulate CVD risks. High levels of plasma LDL-C are directly related to the development of CVD, whereas an inverse association between the incidence of CVD and high concentrations of HDL-C has been observed (Castelli, 1992, 1996).

On the other hand, cholesterol-induced oxidative stress is one of the factors that links hypercholesterolemia with atherogenesis (Halliwell, 1996) and is known to produce vascular atherosclerotic lesion and increased oxidative stress in several tissues (Balkan, 2002), including the development of atherosclerosis in the vascular wall through the formation of reactive oxygen species (ROS) (Byon, 2008; Shi *et al.*, 2000). Oxidative modification of LDL have been postulated to play a pivotal role in atherosclerotic process (Bentley, 2002; Steinberg and Witztum, 2002) and has been implicated at both the early and late stages of the pathogenesis of atherosclerosis, during which plaque rupture leads to further clinical events.

Besides classical risk factors such as hypercholesterolemia and hypertension; chronic subacute inflammation has been recognized as an important force driving the development of atherosclerosis (Khovidhunkit *et al.*, 2004). Therefore, involvement of inflammation in atherosclerosis has spurred the discovery and adoption of inflammatory biomarkers for cardiovascular risk prediction. Two hypothesis have been proposed to explain the role of inflammatory markers in the pathogenesis of atherosclerosis. One mechanism may be the ongoing inflammation in the artery, stimulated by the oxidized-low-density lipoprotein (ox-LDL), which leads to the production of cytokines that may induce the various acute phase proteins. Alternatively, chronic elevations of acute phase reactants could be due to smoking, chronic infections, obesity and hypercholesterolemia, all of which contribute to the development of atherosclerosis. The second one is hyperlipidemia induced atherosclerosis.

In order to reduce the progression of CVDs in the body, different drugs such as statins are used frequently. Statins specifically inhibit the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which is the rate limiting enzyme of the cholesterol synthesis (Daniel Pella *et al.*, 2005). As it happens with all chemical drugs, long term use of statins also have host of side effects and may incurve problems in terms of toxicity and cost. Therefore, drugs derived from natural products could be a good alternative in the treatment and management of atherosclerosis. Number of studies has demonstrated the role of natural products in inhibiting the HMG-CoA reductase acitivity (Iqbal *et al.*, 2014a; Reddy et al., 2014; Iqbal *et al.*, 2014b) and hypercholesterolemia (Iqbal *et al.*, 2015) as well as atherosclerosis (Khan *et al.*, 2011; Orekhov and

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Tertov, 1997). A plant dominated diet mainly has multiple nutrients such as vitamins, carotenoids, and flavonoids that may influence the risk of CVD by preventing the oxidation of cholesterol in arteries. Carotenoids are mainly derived from entire plant such as roots, stems, leaves and flowers. Human blood and tissues have measurable concentrations of approximately 12 carotenoids that account for most of the dietary intake (Crews *et al.*, 2001; Stahl and Sies, 1996). The most common of the carotenoids are: lycopene, lutein, α-carotene, β-carotene, β-cryptoxanthin and zeaxanthin (Stahl and Sies, 1996). Among these, lycopene received much attention over the world due to its potential antioxidant and antiatherosclerotic properties.

2. Lycopene and its biochemistry

Lycopene, the most abundant carotenoid present in human plasma and synthesized by plants and microrganisms, is an acyclic isomer of beta-carotene (Rao and Agarwal, 1999; Clinton, 1998) arranged in a linear array having 11 conjugated and two non-conjugated double bonds (Britton, 1995; Zechmeister *et al.*, 1991). It mainly exists in all-*trans* configurations which is the most thermodynamically stable form of lycopene (Figure 1). In human plasma, lycopene is present as an isomeric mixture having 50% as *cis*-isomers (Clinton *et al.*, 1996). It is known to be the most potent antioxidant having high number of conjugated dienes and a singlet-oxygen-quenching ability which is two times higher as that of β-carotene and 10 times higher than that of α-tocopherol (Miller *et al.*, 1996; Mortensen and Skibsted, 1997; Woodall *et al.*, 1997; Di Mascio *et al.*, 1989). Since, lycopene and other carotenoids are lipophilic in nature, they are found to concentrate in serum LDL and very-low-density lipoprotein (VLDL) fractions (Clinton *et al.*, 1996) as well as it also concentrates in the adrenal gland, testes, liver and prostate gland (Stahl *et al.*, 1992; Nierenberg and Nann, 1992). The distribution of lycopene is tissue-specific which may play an important role in antioxidant operation. Lycopene mainly occurs in red fruits and vegetables, including tomatoes, watermelons, pink grapefruits, pink guavas and apricots.

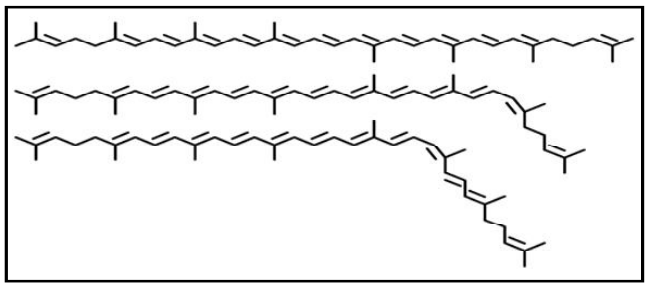

Figure 1: Chemical structure of the most common lycopene isomers.

3. Bioavailability of lycopene

The bioavailability of lycopene changes greatly in different food sources. The absorption of lycopene may be lower when raw tomato, different tomato products and certain fruits are consumed. Processing and cooking of food significantly enhances the bioavailability of lycopene by disrupting its binding patterns to matrices and converting the highly lipophilic lycopene easily available for intestinal absorption (Unlu *et al.*, 2005; Unlu *et al.*, 2007). The study of role of lycopene in human health and nutrition is very much complicated because the main dietary source of lycopene (*i.e.*, tomatoes) mainly consist of all-*trans* isomers, but blood, plasma and different tissues contain relatively higher concentrations of *cis*-isomers (Campbell *et al.*, 2007). The processing and cooking of tomatoes by heating convert the all-*trans* lycopene to a range of its *cis*-isomers which are regarded as being more bioavailable due to their higher solubility and much better absorption from the lumen of intestine than all-*trans* isomer (Boileau *et al.*, 2002). Different other studies demonstrated that gastrointestinal lumen (Moraru and Lee, 2005; Boileau *et al.*, 1999), liver (Teodoro *et al.*, 2009), and enterocytes (Richelle *et al.*, 2010) were potential sites for the isomerisation of lycopene *in vivo*.

4. Lycopene and hyperlipidemia

Hypercholesterolemia is one of the important risk factors for atherosclerosis progression and other cardiovascular complications. In recent years, lycopene has been suggested to have beneficial effects against such disease, although the exact molecular mechanism behind it is still unknown. Human body maintains cholesterol homeostasis through the coordinated regulation of pathways mediating cholesterol uptake, storage, *de novo* synthesis and efflux. Deregulation of these signals results in foam cell formation (Brown and Goldstein, 1986). The rate limiting step in the biosynthesis of cholesterol is catalyzed by HMG-CoA reductase (Edwards and Ericsson, 1999; Istvan, 2001) that promotes the deacylation of HMG-CoA to mevalonate (Istvan and Deisenhofer, 2001). HMG-CoA reductase activity in animal cells has been shown to be sensitive to sterols and non-sterol products of the mevalonate pathway (Brown and Goldstein, 1980; Bilheimer *et al.*, 1989). As sterols do, lycopene can also reduce the level of cholesterol synthesis in cell cultures by inhibiting HMG-CoA reductase enzyme (Fuhrman *et al.*, 1997) or by decreasing expression of this enzyme (Palozza *et al.*, 2011). In addition, hypocholesterolemic effect of lycopene was accompanied by a decrease in the activity of hepatic HMG-CoA reductase enzyme. The inhibition of HMG-CoA reductase by lycopene may involve the inhibition of this enzyme at a post-transcriptional level (Inmaculada *et al.*, 2014). Since, lycopene and other carotenoids are polyisoprenoids, synthesized in plants from mevalonate *via* the HMG-CoA reductase pathway, they may act as competitive inhibitor of this enzyme (Gark and Douglas, 1983). This inhibitory mechanism of lycopene was confirmed using the molecular modelling method, which clearly showed that the HMG-CoA reductase substrate-binding pocket accommodates lycopene molecules following competitive inhibition of the HMG-CoA reductase. Lycopene may interact with the active site of HMG-CoA reductase to form a complex which is similar to that formed between the substrate HMG-CoA reductase and the cerivastatin or any other inhibitor with the enzyme. Lycopene competes with HMG-CoA reductase, thus altering mevalonate formation and consequently reducing cholesterol synthesis (Inmaculada *et al.*, 2014).

Studies indicated that lycopene can effectively decrease the elevated levels of serum total cholesterol (TC), triglyceride (TG) and LDL cholesterol in high fat diet (HFD) induced atherosclerosis in rabbits and also suppresses atherogenesis with a significant effect equivalent to that of fluvastatin (Hu *et al.*, 2007; Hu *et al.*, 2008). Moreover, TG, LDL, TC levels were decreased and the HDL-C levels were increased significantly on treatment with cis/all-trans 40:60 algal lycopene (AL) (Renju *et al.*, 2014). Lorenz *et al.* (2012) also observed a significant reduction to nearly 50% of the TC and LDL cholesterol rabbit's serum levels in the lycopene treated group when

compared to that of high-cholesterol and the placebo groups. Fuhrman *et al.* (1997) suggested that hypocholesterolemic action of lycopene was due to suppressing the cholesterol synthesis and to augment the LDL receptor activity in macrophages.

5. Lycopene and smoking induced atherosclerosis

Endothelial injury is one of the important determinants of atherosclerotic process and mainly causes the thickening of intima of arteries. There are number of factors seem to be causative in endothelial dysfunction such as endotoxins, hypoxia, specific endothelial toxins such as homocysteine, number of possible viruses or other infectious agents and cigarette smoke derived products (Puddu *et al.*, 2009). Cigarette smoking causes atherosclerosis to occur at earlier age regardless of vascular bed, whereas stopping smoking delays the onset of atherosclerosis (Willium and Feeman, 1999). Cigarette smoking stimulates all phases of atherosclerosis from endothelial injury and dysfunction to acute clinical events, increasing oxidation of LDL cholesterol and reducing blood levels of HDL cholesterol. It also impacts enhancing blood levels of adhesion molecules and fibrinogen which may lead to platelet aggregation and eventually to vascular spasm (Vardavas and Panagiotakos, 2009). Experimental data of many studies support the hypothesis that lycopene may act as a protective agent against cigarette smoke exposure by reducing smoke-induced oxidative stress and by regulating molecular pathways involved in cell proliferation, differentiation, inflammation and apoptosis (Palozza *et al.*, 2005). Another study showed that lycopene attenuates endothelial dysfunction in streptozotocin-induced diabetic rats by reducing oxidative stress (Jing Zhu *et al.*, 2011). Moreover, lycopene strongly inhibited cell growth in immortalized fibroblasts, exposed to cigarette smoke condensate, by arresting cell cycle progression and by promoting apoptosis (Palozza *et al.*, 2005).

Low serum lycopene and β-carotene level increases risk of acute myocardial infarction in men (Jouni *et al.*, 2011). Dietary intake of lycopene *via* vegetable and fruit ingestion in smokers demonstrated that lycopene significantly reduces oxidative stress and ameliorates endothelial function (Pennathur *et al.*, 2010). In a prospective, nested case-control study using WHS database, 483 cases of CVD were compared to an equal number of controls free of CVD and matched for age, follow-up time (4.8 yr), and smoking status (Sesso *et al.*, 2004). Data analyse from this study, revealed that higher plasma lycopene concentrations were inversely associated with a risk of CVD in middle-aged and elderly women. Moreover, another nested case-control study demonstrated that baseline plasma levels of lycopene (as well as α-carotene or β-carotene) tended to be inversely related to risk of ischemic stroke showing an apparent threshold effect (Hak *et al.*, 2004). Beneficial effects of tomato lycopene on the risk of smoke related pathologies such as cardiovascular injury and cancer have also been demonstrated (Palozza *et al.*, 2008). However, the scientific rationale for such health benefits is not fully understood. One of the possible mechanisms for the protective activities of lycopene in smoke-related pathologies is by down-regulation of the cigarette smoke-stimulated inflammatory response (Palozza *et al.*, 2010). In fact, the carotenoid has been reported to inhibit pivotal proinflammatory mediators, including ROS (Mascio *et al.*, 1989) and cytokines (Britton, 1995) and to affect signal transduction pathways involved in inflammatory processes.

6. Inhibition of foam cell formation

Atherosclerosis is a major cause of morbidity and mortality in developed societies, and initiates when activated endothelial cells (ECs) recruit monocytes and T-cells from the bloodstream into the arterial wall. Macrophages that accumulate cholesterol and other fatty materials are transformed into foam cells (Zolberg *et al.*, 2015). Lycopene may diminish modified LDL induced macrophage foam cell formation by declining lipid synthesis and down regulating the activity and expression of scavenger receptor-A (SR-A). However, these possessions are accompanied by abnormal secretion of the anti-inflammatory cytokine interleukin (IL) -10, suggesting that lycopene may also exert a concomitant proinflammatory effect (Pascale *et al.*, 2007). Results from a recent study indicate that dietary carotenoids, such as 9-cis β-carotene, accumulate in macrophages and can be locally cleaved by endogenous β-carotene 15, 15'-monooxygenase (BCMO1) to form 9-cis retinoic acid and other retinoids and these retinoids activate the retinoid X receptor (RXR), a nuclear receptor, that along with additional nuclear receptors, can affect various metabolic pathway including those involved in foam cell formation and atherosclerosis (Zolberg *et al.*, 2015). Another study demonstrated that this carotenoid significantly inhibited cholesterol esterification during foam cell development in human monocyte-derived macrophages (Napolitano *et al.*, 2007).

7. Lycopene in inflammatory modulation

The process of inflammation often common in CVD patients is initiated by several inflammatory mediators, of which the transcription factor nuclear factor-kappa B (NF-κB) plays a major role (Baker *et al.*, 2011). ROS can activate the transcription factor NF-κB that gives rise to the expression of pro and anti-inflammatory cytokines genes and their subsequent production (Hayden *et al.*, 2006). Lycopene possesses the inhibitory effect on the activation of pro and anti-inflammatory cytokines (Gouranton *et al.*, 2011; Simone *et al.*, 2011). A variety of carotenoids, including lycopene and lutein also known to inhibit cytokine production *via* suppressing ROS stimulated NF-κB activation (Kim *et al.*, 2004; Armoza *et al.*, 2012; Bai *et al.*, 2005; Kim *et al.*, 2008). Moreover, lycopene has been found to stimulate the production of anti-inflammatory cytokines such as IL-10, which controls the inflammation and also inhibits the production of proinflammatory cytokines including tumor necrosis factor-alpha (TNF-α), IL- 6, and IL-8 which increase the inflammatory response (Feng *et al.*, 2010). Significant decreased levels of IL-6 were observed in mice with adipose tissue inflammation when treated with lycopene (Gouranton *et al.*, 2011). It has also been demonstrated that lycopene can suppress the expression of inflammatory cytokines and reverse the loss of antioxidant enzymes activity induced by inflammation, either by injecting with lipopolysaccharide or by exposure to iron (Kim *et al.*, 2004; Reifen *et al.*, 2004; Riso *et al.*, 2006). Moreover, the levels of inflammatory marker enzymes like cyclooxygenase, 15-lipoxygenase in monocytes and myeloperoxidase (MPO), C-Reactive Protein (CRP) and ceruloplasmin in serum were found to be decreased after treatment with algal lycopene (Renju *et al.*, 2014). A placebo-controlled, double-blind, crossover study on healthy human volunteers showed that 5.7 mg of lycopene for 26 days effectively reduced inflammation and inhibited the production of TNF-α (Riso *et al.*, 2006). In addition, lycopene also stimulated the production of the anti-inflammatory cytokine IL-10 (Hazewindus *et al.*, 2012).

8. Antilipoperoxidative/antiatherosclerotic property of lycopene

Lipid peroxidation is the process of oxidative degradation of lipids in which free radicals steal electrons from the lipids in cell membranes, resulting in cell damage. This process initiates by a free radical chain reaction mechanism and most often affects polyunsaturated fatty acids, because they contain multiple double bonds in between which lie methylene bridges (-CH_2-) that possess especially reactive hydrogens. Lycopene is known to be a strong free radical scavenger (Pennathur *et al.,* 2010) and studies also demonstrated its antilipoperoxidative action (Esterbauer and Ramos, 1995). Elmadfa *et al.* (2004) and Riso *et al.* (2004) demonstrated significant reduction in plasma-conjugated dienes and malondialdehydes (MDA) levels after 3 weeks supplementation of lycopene or β-carotene. Moreover, plasma carotenoids inversely correlated with IL-6 and conjugated dienes, though not with CRP (Markovits *et al.*, 2009). Another study showed that the ratio of serum total antioxidant capacity (TAC) to MDA improved significantly in the group treated with lycopene when compared to the placebo group (Neyestani *et al.*, 2007). Furthermore, thiobarbituric acid (TBA) reactive substances levels were also found to be decreased in algal lycopene treated hyperlipidemic rats when compared to the lovastatin treated rats (Renju *et al.,* 2014). Matos *et al.* (2006) demonstrated that lycopene injection for five days with a dose level of 10 mg/kg/day causes the significant reduction in lipid peroxidation and an increase in prostate tissue protection against Fe^{2+}-induced oxidative damage.

Oxidative modification of lipoproteins and high concentrations of LDL in serum represent a major risk factor for atherosclerosis; play an important role in the initiation and progression of atherosclerotic lesion development. Oxidized LDL (Ox-LDL) acts through the interaction with several scavenger receptors, expressed differentially on the surface of different cells of the arterial wall and inflammatory circulating cells involved in the atherosclerotic process (Sawamura *et al.,* 1997). In the cytosolic compartment, immediate targets of reactive oxygen species (ROS) are long-chain free fatty acids and membrane-bound lipids leading to the lipid peroxides formation. LDL is now recognized to critically contribute to the pathogenesis and progression of human atherosclerosis. Free radicals mainly attack plasma LDL and convert it to Ox-LDL forms leading to the attraction of blood monocytes beneath the endothelium. Ox-LDL is highly atherogenic in nature as it stimulates cholesterol accumulation in macrophages and foam cell formation. Both these events are toxic to cells of the arterial wall and give rise to inflammatory and thrombotic processes (Albertini *et al.,* 2002).

Several theories exist on the mechanisms by which LDL induces atherosclerosis. The level in the body, the size and the chemical modification of LDL are very important measures for atherogenesis (Albertini *et al.,* 2002). LDL undergoes chemical modification after its synthesis to produce modified LDL. Modification of LDL occurs in either plasma or in the inner layer of the artery and affected either the lipid or the protein fraction. This modification is mainly induced by hydrolytic or proteolytic enzymes, oxygen radicals or other non-enzymatic mechanisms. This chemically modified LDL is then taken up by receptors or scavenger receptors present on monocytes/macrophages, kupffer cells and endothelial cells. Ox-LDL represents the most important chemically modified LDL whereas glucosylated LDL is more susceptible to oxidation than normal LDL (Napoli *et al.,* 1997).

Lycopene is thought to be the major nonenzymatic antioxidant found in the lipid derived structures of cells and lipoproteins. It is a donor antioxidant, which involve in increasing LDL resistance against the oxidative modification. In lipid solutions and dispersions, lycopene inhibits formation of free radical linearly with time until consumed in the process (Rissanen *et al.,* 2000). Depending on the dose at which it is administered, lycopene has been shown to act as a potent antioxidant or a pro-oxidant (Yeh and Hu, 2000). Number of *in vitro* studies have shown potential role of lycopene or tomato extracts in delaying chemically induced LDL oxidation lag time (Petr and Erdman, 2005; Esterbauer *et al.,* 1992). Being a major carotenoid in human plasma, lycopene also inhibits the oxidative modification of isolated LDL (Fuhrman *et al.,* 1997). It has been also observed that treatment of lycopene alone rarely significantly decreases the serum lipid peroxidation or *in vitro* LDL oxidation (Esterbauer *et al.,* 1992; Dugas *et al.,* 1999) whereas; interactions of lycopene with other nutrient compounds have been reported to strongly reduce LDL oxidation (Petr and Erdman, 2005). Furthermore, lycopene in combination with vitamin E (α-tocopherol) resulted in inhibiting the Cu^{++}-induced LDL oxidation that was significantly greater than the expected additive individual inhibitions (Fuhrman *et al.,* 2000). Three-weeks supplementation study of tomato products (raw, sauce, and paste) on twelve females have found an increased significant lycopene concentrations and a reduced LDL-oxidizability suggesting an important role for tomato products in the prevention of lipid peroxidation (Visioli *et al.,* 2003). In another study, lycopene in combination with rosmarinic acid, glabridin, carnosic acid, or garlic demonstrated synergistic antioxidative effects against LDL oxidation induced either by copper ions or by the radical generator, 2,2¹-diazobis-(2-amidinopropane)-dihydrocloride (AAPH) (Fuhrman *et al.,* 2000). Another study indicated that ascorbic acid, α-tocopherol and lycopene can also inhibit LDL carbamylation and, therefore, may have a role in ameliorating atherosclerotic risk for patients with kidney failure (Ghaffari *et al.,* 2010). It has also been suggested that lycopene can protect human LDL against lipid peroxidation more efficiently than other carotenoids, even though it is present in LDL in much lower concentrations (Esterbauer and Ramos, 1995). Similarly, lycopene alleviates the antioxidant enzymes activities, *viz.* catalase, superoxide dismutase, glutathione peroxidase, and glutathione reductase activities in algal lycopene administered hyperlipidemic rats when compared to the lovastatin treated rats (Renju *et al.,* 2014).

9. Lycopene and smooth muscle cell proliferation

Irregular proliferation of vascular smooth muscle cells (VSMCs) is one of the most important factors which play a central role in the progression of atherosclerosis. A large number of studies have revealed that VSMCs are the major cells in atherosclerotic plaques (Faries *et al.,* 2002). Platelet-derived growth factor (PDGF) is a powerful stimulator of growth and motility of smooth muscle cells (SMCs) and fibroblasts. Abnormalities of PDGF/PDGF receptor (PDGFR) are associated with vascular diseases and malignancy. A recent study demonstrated that lycopene interacts with PDGF-AA/-AB and compromises their intracellular signaling, leading to a striking inhibition on PDGF-AA/-AB-induced migration in both SMCs and fibroblasts. They also predicted its binding region within PDGF and proved its antivascular injury effect *in vivo* (Ching-Pei *et al.,* 2010).

10. Conclusion

Based on the above data review, it has been concluded that number of studies have been done to depict the role of lycopene in atherosclerosis/CVD. Moreover, in view of statin induced host of side effects, the current research paradigm has been shifted towards natural products which are safer as well as provide nutritional value. Only few studies pointed out the hypocholesterolemic action of lycopene, in fact the mechanistic aspect is lacking. Since, it is well described that number of risk factors are involved in atherosclerosis progression and subsequent CVD, solo natural agent, like lycopene, with multiple therapeutic properties might be beneficial in treatment and management of risk factors induced atherosclerosis. A proposed hypothesis for lycopene mediated pleiotropic protection against risk factors induced atherosclerosis is illustrated diagrammatically (Figure 2).

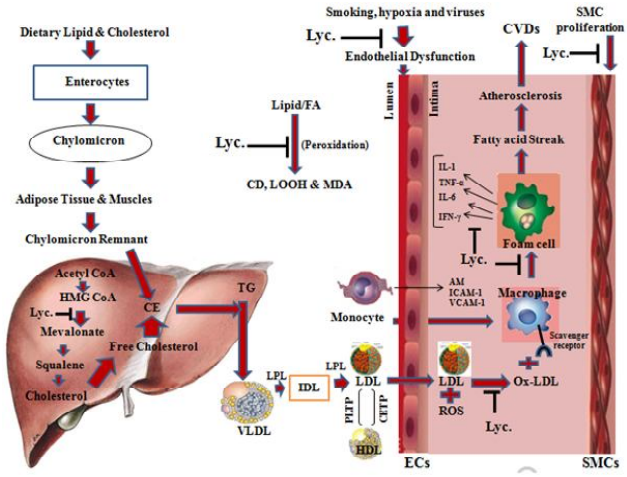

Figure 2: Possible mechanisms of lycopene in prevention of various risk factor induced atherosclerosis.

Conflict of interest

We declare that we have no conflict of interest.

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