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## Review article:

# WATERMELON LYCOPENE AND ALLIED HEALTH CLAIMS

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## ABSTRACT

Presently, functional foods and nutraceuticals are gaining immense importance in the prevention of various maladies through dietary regimen module. Consumption of fruits and vegetables based diet has pursuit a range of bioactive components, especially phytochemicals targeting life threatening ailments. In this context, lycopene is an extensively studied antioxidant potentially present in watermelon, tomato, pink guava etc. Watermelon is one of the unique sources having readily available *cis*-isomeric lycopene. The distinctive aroma of watermelon is imparted by medium- and short-chain fatty acids along with geranial, β-ionone and neral. Its consumption has been escalated owing to rich nutritional profile and allied health benefits. It is effective in reducing the extent of cancer insurgence, cardiovascular disorders, diabetes and macular diseases. The structural characteristics, physiochemical properties and therapeutic effects of lycopene are the limelight of the manuscript. However, further research investigations are still needed to address the health enhancing potential of watermelon lycopene.

**Keywords:** Functional foods, watermelon, lycopene, cancer, cardiovascular disorders, macular diseases

## BACKGROUND

Accumulating evidences have established a consensus that fruits are concentrated source of natural components thus having health promoting properties (Butt et al., 2008). Plant based diet contains several bioactive ingredients with vital role to perform various metabolic functions like growth, development and protective mechanism against physiological threats. In this context, phytochemicals are of significance importance as they improve the human health through distinct pathways. The plants that are rich sources of bioactive molecules include garlic, ginger, tea, ginseng, black cumin, mulberry, raspberry etc. (Butt et al., 2009). Researchers are focusing on exploitation of natural resources for dietary regimen against life threatening ailments (Lucier and Lin, 2001).

Watermelon (*Citrullus lanatus*), botanically considered as a fruit, belongs to the family *Cucurbitaceae* (Edwards et al., 2003).

It is native to Kalahari desert of Africa but nowadays, it is also cultivated in tropical regions of the world. In the pages of history, its first harvest was documented 5000 years ago in Egypt that later spread to other part of the world. Presently, China is the top producer followed by Turkey, United States, Iran and Republics of Korea (Zohary and Hopf, 2000; Lucier and Lin, 2001; Naz et al., 2013). Watermelon is a valued source of natural antioxidants with special reference to lycopene, ascorbic acid and citruline. These functional ingredients act as protection against chronic health problems like cancer insurgence and cardiovascular disorders (Zhang and Hamauzu, 2004; Omoni and Aluko, 2005; Fenko et al., 2009). Lycopene is characterized by its distinctive red color in fruits and vegetable (Mutanen and Pajari, 2011).

During the last few decades, presence of appreciable quantity of lycopene in watermelon has motivated the farmers/growers to cultivate high red flesh varieties. Overall, twelve hundred cultivars of watermelon are produced worldwide while the four most promising cultivars are picnic, icebox, yellow flesh and seed less (Chalabi et al., 2006; Helyes et al., 2009). This review article intends to enlighten the readers regarding rich nutritional profile of the watermelon with special focus on lycopene and its therapeutic aspects like prevent oxidative stress, cancer, hypercholesterolemia, diabetes and macular disorders.

## CLASSIFICATION AND NUTRITIONAL PROFILE

Watermelon (*Citrullus lanatus*) has association with cucumber, pumpkin, squash and gourds; belonging to family *Cucurbitaceae* (Edwards et al., 2003). Fruit of this plant is major consumed portion and variations in growth characteristics determine its end use quality (Maynard, 2001; Oms-Oliu et al., 2009a). Considering the nutritional profile, consumption of 100 g watermelon provides 30 kcal. It contains almost 92 % water and 7.55 % of carbohydrates out of which 6.2 % are sugars and 0.4 % dietary fiber. It is enriched with carotenoid, vitamin C, citrulline, carotenoids and flavonoids and fat and cholesterol free, thus considered as low caloric fruit (Leskovar et al., 2004; Bruton et al., 2009). Additionally, watermelon is rich source of β-carotene acts as an antioxidant and precursor of vitamin A.

Besides the presence of lycopene, it is a source of B vitamins, especially $B_1$ and $B_6$, as well as minerals such as potassium and magnesium (Huh et al., 2008). Watermelon contains phenolics quite comparable with that of other fruits (Kaur and Kapoor, 2001; Jaskani et al., 2005). It is an inexpensive and nutritious source that is readily available to all socio-economic groups of Pakistan throughout the summer season. Its consumption depends on number of factors e.g. availability, income, age, gender, racial and ethnic norms. In this context, per capita consumption in Asian communities is almost 3 times greater as compared to other part of globe (Dermesonlouoglou et al., 2007).

**BOTANICAL CLASSIFICATION OF WATERMELON**

| | |
|---|---|
| Kingdom | *Plantae* – Plant |
| Subkingdom | *Tracheobionta* - Vascular plants |
| Superdivision | *Spermatophyta* - Seed plants |
| Division | *Magnoliophyta* - Flowering plants |
| Class | *Magnoliosida* – Dicotyledons |
| Order | *Cucurbit ales* |
| Family | *Cucurbitaceae* |
| Genus | *Citrullus* |
| Species | *Citrullus lanatus* |

## AROMA CONTRIBUTING VOLATILES

In various fruits, flowers and spices monoterpens and norisoprenoids (apo-carotenals) are the key compounds producing characteristic scent. In case of watermelon, distinctive aroma is imparted by medium- and short-chain fatty acids along with geranial, β-ionone and neral that are some of the norisoprenoid and monoterpene compounds. However, esters are absent unlikely as in most fruits *i.e.* strawberry, banana, melon etc. (Tadmor et al., 2005). *In-vitro* evidences have supported that fruit scents are degraded carotenoids by the action of lipoxygenases, peroxidases and dioxygenases. However, it is also interesting to know that citral that is an aromatic compound of lemon grass, lemon basil and various lemon scented plants is a combination *cis*- and *trans*- monoterpene, neral and geranial. Several gathered information have supported its biosynthesis in lycopene rich fruits as in watermelon and tomato (Micol et al., 2007).

## WATERMELON: A POTENTIAL SOURCE OF LYCOPENE

Earlier, only tomato and its products were considered as potential sources of lycopene but now there are proven facts that watermelon also contains appreciable amount of *cis*-configured lycopene. Thus consumer is gradually shifting towards watermelon and its allied products for their health concerns. Nevertheless, the quantity of lycopene varies depending upon the variety and growing conditions (Fish and Davis, 2003). Overall, lycopene ranges from 2.30-7.20 mg/100 g fresh weight bases, present in crystalline form in cell (Huh et al., 2008; Chaoensiri et al., 2009; Artes-Henandez et al., 2010). More interestingly, lycopene contents of red fleshed watermelon are almost 40 % higher than tomato *i.e.* 4.81 and 3.03 mg/100 g, respectively. However, yellow orange and yellow colored fleshed have relatively less lycopene content *i.e.* 3.68 and 2.51 mg/100 g, respectively (Jaskani, 2005; Choudhary et al., 2009). In tomato, lycopene is available in relatively higher quantity after heat treatment due to break down of protein-carotenoid complex. In contrast, lycopene from watermelon is available directly to the human body just after consumption (Edwards et al., 2003; Perkins-Veaize and Collins, 2004; Jaskani et al., 2006; Saftner et al., 2007).

Storage conditions are also cardinal that significantly affect the concentrations of lycopene, phenolics and vitamin C contents. The higher ratio of lycopene to carotene in watermelon *i.e.* 1:12 yields remarkable antioxidant capacity (Mort et al., 2008). Owing to this specific characteristic, foods high in lycopene contents are referred as functional foods (Shi and Maguer, 2000; Collins et al., 2005; Jiang and Lin, 2007; Davis et al., 2008).

## SYNTHESIS ROUTE OF LYCOPENE

A complex mechanism persists in the biosynthesis of lycopene that starts when chlorophyll degrades to yield white colored leucoplast thus yielding specialized red color pigmented organelles *i.e.* chromoplast (Bowen et al., 2002). Lycopene is a carotenoid that is produced as an intermediate product of xanthophylls production; β-cryptoxanthin, zeaxanthin, leutin etc. Carotenoids are basically formed by 40-C isoprenoids (5-C isoprene unit), called tetraprenoids. A stepwise addition of isopentenyl diphosphate (IPP) takes place with dimethylallyl diphosphate (DMAPP) giving rise 20-C precursor, geranylgeranyl diphosphate (GGPP). On desaturation of GGPP, 11 conjugated double bonds are produced that exist as lycopene in nature. From this point cyclic conversion takes place converting it to α- and β-carotene that on oxidation produce xanthophylls (Ishida and Bartley, 2005).

Lycopene crystals are in voluminous red color found in the form of small globules suspended throughout the fruit (Chandrika et al., 2009). At cellular level lycopene is present in thylakoid membrane as protein-lycopene complex due to its lipophilic nature. It is well documented that lycopene is

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present in all-trans form within the fruit that is transformed from *cis*-configured lycopene due to the action of carotenoid isomerase enzyme. However, in case of watermelon absence of this enzyme keep it in its *cis*-form (Akhtar et al., 1999; Bangalore et al., 2008).

## LYCOPENE: STRUCTURE AND PHYSICOCHEMICAL PROPERTIES

Lycopene is a vibrant tetrapenic carotenoid with molecular formula of $C_{40}H_{56}$ (Figure 1) and contains 11 conjugated and 2 unconjugated double bonds (Fish et al., 2002). It is an acyclic isomer and open-chain analogue of β-carotene that undergoes *cis-trans* isomerization when interact with light, temperature and chemicals (Ollanketo et al., 2001). A great majority of studies have demonstrated that human blood serum contains both *cis*- and *trans*- isomeric forms of lycopene whereas the plants have only trans-configuration except watermelon (Klipstein-Grobusch et al., 2000; Tadmor et al., 2005). Some isomeric forms of lycopene are also depicted in Figure 1. Among different configurations, 5-*cis* form is more stable with strong antioxidant potential as compared to all-trans, 7-*cis*, 9-*cis*, 11-*cis*, 13-*cis* and 15-*cis* (Arab and Steck, 2000; Chasse et al., 2001; Lewinsohn et al., 2005; Alquézar et al., 2009).

Numerous publications have reported that the amount of lycopene affected significantly as a function of storage time and temperature of watermelon. It has been observed that the lycopene content at storage temperature of 5° C varied from 7.8 to 8.1 mg/100 g that increased to 8.1 to 12.7 mg/100 g at 20° C (Mokbe, 2005; Choudhary et al., 2009). Data from various studies have shown an increasing trend of lycopene and β-carotene contents of watermelon at higher storage temperatures. It has been suggested that the carotenoids producing enzymes pathways are sensitive to temperature (Oms-Oliu et al., 2009b). The details of physical properties of lycopene are given in Table 1.

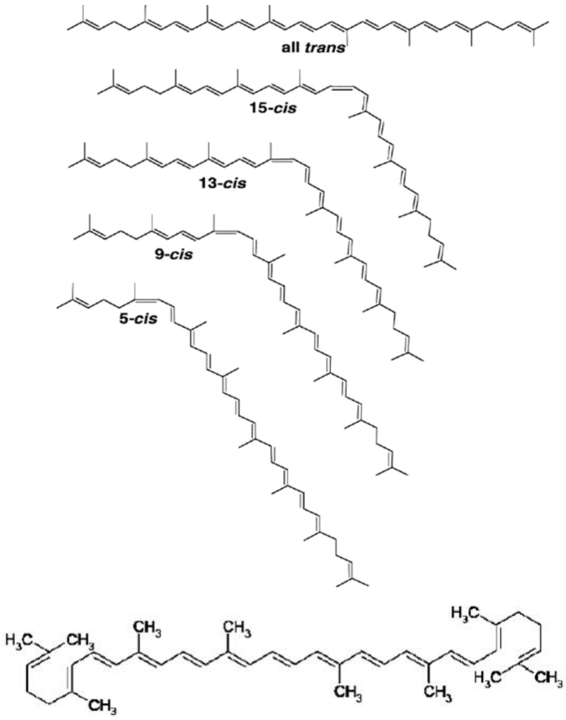


**Figure 1:** *Trans*- and *cis*- isomers of lycopene

**Table 1:** Physical properties of lycopene

| | |
|---|---|
| Chemical formula | $C_{40}H_{56}$ |
| Melting point | 172 to 175ºC |
| Precipitate form | Deep reddish-brown |
| Crystalline shape | Long red needles from a mixture of carbon disulfide and ethanol |
| Sensitivity | Light, high temperature, oxygen, acids |
| Solubility | Soluble in non-polar solvents e.g. chloroform, hexane<br>Insoluble in polar solvents *i.e.* water, methanol and ethanol |

(Shi and Maguer, 2000)

## ABSORPTION PATHWAY

Lycopene efficiently absorbs when supplemented with fat owing to its lipophilic characteristics (Rao and Agarwal, 1999). Its assimilation is dependent on chylomicron micells mediated mechanism, facilitates its movement from gastrointestinal tract towards body tissues. The isomeric form of lycopene also affects the absorption e.g. *trans*-isomeric form is less adsorbed as compared to *cis*-isomeric configuration (Collins et al., 2005; Rupasinghe and Clegg, 2007). Presences of fat as well as *cis*-isomeric forms facilitate lycopene absorption afterwards, it resides in the adipose tissues, liver, prostate and adrenal glands. After ingestion of lycopene-based food, disruption carotenoids occur within the low pH environment of stomach where lycopene get attached to the protein to pass through intestinal leumen. The resultant lycopene-protein complex breakdown and lycopene joins chylomicron in blood stream from where it goes to target tissue via hepatic pathway (Jian et al., 2005; Gao et al., 2008). The detailed mechanism of lycopene absorption and its storage is described in Figure 2.

## LYCOPENE HEALTH CLAIMS

Lycopene has potential to prevent various chronic ailments like dyslipidemia, diabetes, oncogenesis, neurodegenerative diseases, osteoporosis etc. The protective aspects are ascribed to the singlet oxygen scavenging ability. Numerous metabolic syndromes arise due to high free radicals formation reacting with macromolecules thus oxidizing proteins, lipids and DNA. Lycopene protects humans from various pathogenic attacks responsible for an array of diseases (Ilic and Misso, 2012; Sesso et al., 2005). Several authors have reported that lycopene holds nutraceutical potential and being antioxidant provides protection against free radicals and oxidative damage (Krinsky, 1998; Rao and Agarwal, 1999; Choksi and Joshi, 2007). Free radicals are produced in the body during oxidation reduction reaction however, excessive production deteriorates body defense mechanism, cell membrane and organelles. These degenerative processes resulted in life threatening ailments (Humberto, 2000; Heber and Lu, 2002; Perkins-Veazie and Collins, 2006). The presence of large number of double bonds is responsible for its fairly high free radical scavenging or singlet oxygen quenching ability even better than α- and β-carotene, lutein and α-tocopherol (Rivero et al., 2001; Perkins-Veazie and Collins, 2004). Lycopene provides protection against degenerative disorders via mechanisms like gap-junction communication, gene function regulation, phase II drug-metabolizing pathways and carcinogenic metabolism (Arab and Steck, 2000; Collins et al., 2004). It has been established through epidemiological studies that lycopene plays a

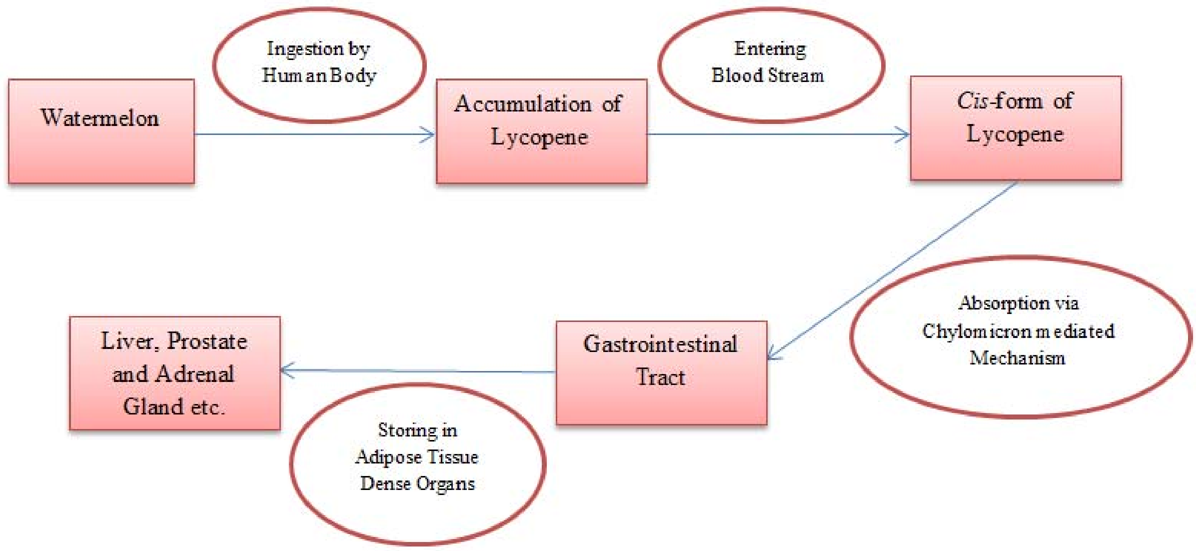


**Figure 2:** Absorption pathway of lycopene

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role in maintaining normal cellular differentiation and division (Giovannucci et al., 2002; Choudhary et al., 2009). Lycopene scavenges free radicals at cellular level due to its attachment in cell membrane thereby may prevent hypercholesterolemia and hyperglycemia along with allied dysfunctions (Marinova et al., 2005; Fisher and Frazee, 2006).

***a.Oxidative stress***

Oxidative stress is an etiological factor in the onset of various metabolic dysfunctions. There are proven facts that uncontrolled oxidation leads to generate excessive reactive oxygen species (ROS), causative agent of many ailments that can address through antioxidants/phytochemicals rich diets (Butt et al., 2009). Excessive production of free radicals leads to atherosclerosis by inactivation of nitric oxide and impairment of endothelium dependent vasodilatation. The ROS are produced continuously in normal metabolic pathways. The diet, smoking, exercises and environmental variables may enhance the production of ROS (Weisburger, 2002; Espin et al., 2007; Migliore and Coppedè, 2009). Despite, antioxidants have ability to start repairing through chain-chain interaction with oxidized biomolecules (Holden et al., 1999; Kauer-Sant'Anna et al., 2009). Diet based therapy indicated a significant role of lycopene in the reduction of oxidative damage of DNA and lymphocytes and short term improvement in LDL oxidation (Alshatwi et al., 2010).

The oxidative balance disrupts during production of reactive oxygen species (ROS) that successively generate double allylic hydrogen atom and initiate oxidation of lipid. Meanwhile, neutrophils catalyze the synthesis of hypochlorous acid that causes oxidative injury in terms of cellular damage. In this milieu, body produces defense enzymes i.e. superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px). Superoxide dismutase acts as first line defense by producing singlet oxygen into hydrogen peroxide. However, GSH-Px and catalase enzymes convert hydrogen peroxide into water. Generally, these enzymes work in harmony but in case of ROS over production, interruption may occur resulting necrosis or apoptosis. In such cases, dietary lycopene acts as a therapeutic agent to combat excessive ROS production (Erdman et al., 2009).

Oxidative stress plays a vital role in the prevalence of chronic diseases. Free radicals are linked with various disease pathogenesis as diabetes, cardiovascular complications, osteoporosis, cancer and cataracts (Ratnam et al., 2006). Lycopene significantly restored the antioxidant enzymes including glutathione peroxidase (GSH-Px), superoxide dismutase (SOD), reduced glutathione (GSH) whilst decreased the levels of lipid peroxide malondialdehyde (MDA) in hypertensive patients (Bose and Agrawal, 2007). Similarly, lycopene was found to be effective in reducing MDA and increasing GSH levels in coronary artery disease (Misra et al., 2006). Later, Kim et al. (2011) examined the effect of lycopene in smoker men with low fruit and vegetable intake through a double blind randomized controlled study. They concluded that lycopene significantly reduces oxidative stress and ameliorates endothelial function (Pennathur et al., 2010).

Likewise, Dogukan et al. (2011) probed lycopene against cisplatin-induced lipid peroxidation and nephrotoxicity in male wistar rats. A significant decrease in renal bax protein was observed in rats administrated on lycopene; an indicator of low oxidative stress. Earlier, Devaraj et al. (2008) determined the response of lycopene supplementation on oxidative stress markers. For the reason, human subjects were provided lycopene for two months following LDL and MDA assessment. Lymphocytes were also analyzed to observe any deleterious effect. Comparison of subjects with lycopene restricted group showed a marked decrease in LDL oxidation and TBAR value i.e. 17 and 21 %, respectively. Previous literature has delineated the protective role of lycopene rich food against DNA damage in normal and cancer cells (Liu et al., 2005; Scolastici

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et al., 2008). Likewise, a reduction in lipid peroxidation products i.e. TBARS (21 %) and DNA damage markers were observed in the fibroblast of monkey. In case of rats, lycopene injection for five days with a dose level 10 mg/kg/day showed reduction in lipid peroxidation and prostate tissue protection against Fe-induced oxidative damage (Matos et al., 2006).

Various interventional studies have described the interaction between reduced dyslipidemia and lycopene consumption. The lycopene rich diets have potential to reduce lipid peroxidation, one of the leading factors of hypercholesterolemia. In a case study, Mackinnon et al. (2011) noticed an inverse association of dietary lycopene with oxidative stress and positive impact on bone integrity. Effect of no lycopene diet was determined in postmenopausal women of 50 to 60 years. Blood serum was analyzed for protein thiols and thiobarbituric-malondialdehyde reactive substances along with bone turn over markers; alkaline phosphatase and cross-linked N-telopeptide. Inferences of research indicated that dietary restrictions of lycopene for one month resulting tremendous increase in oxidative stress biomarkers with allied bone resorption.

Similarly, a study was conducted in human subjects to find out the role of lycopene enriched functional juice and vitamin C. The core objective was to measure the effect of lycopene (20.6 mg/day) and vitamin C (435 mg/day) against the biomarkers of inflammation and oxidative stress. Blood serum was examined for lipid status, TBAR and antioxidant capacity. The decrease in TBAR (19 to 22 %) and rise in glutathione value (17 to 20 %) was recorded. It has been observed that functional juice led to a decline in total cholesterol (Jacob et al., 2008). A completely randomized cross over study was conducted to probe the role of lycopene in suppression of oxidative stress using lycopene based capsules. Purposely, twelve healthy subjects were administrated on these capsules and a reduction in lipid oxidation was observed. The oxidative stress biomarkers i.e. TBAR and glutathione showed significant changes. The glutathione value raised up to 23.6 %, whereas, a decrease of 20 % in TBAR value was noticed (Rao and Shen, 2002). Lycopene attenuates lifestyle related disorders without imparting any deleterious effects on hematological aspects. Accordingly, Jonker et al. (2003) conducted a three months study to investigate any toxic effect of lycopene in wistar rats. Blood assay was performed to evaluate the red and white blood cell count, hemoglobin, thrombocytes, neutrophils, lymphocytes and monocytes. The summary of hematological aspects revealed non-significant effect of lycopene supplementation. Moreover, histopathological examination did not reflect any adverse sign. The health benefits of lycopene are depicted in Figure 3.

***b. Nutrigenomics and cancer insurgence***

Presently, a number of evidences are available indicating direct linkages between food active components and cell genomic with special reference to cancer treatment. Nutrigenomics is a broader term that explains interaction of nutrient with gene expression. Being active dietary component, lycopene interferes at various stages of cancer development *i.e.* DNA mutation and tumor metastasis thus have direct impact on gene and inhibit mutation (Nahum et al., 2001). However, understanding of lycopene and gene interaction has not yet been well established and needs further research. Lycopene is likely to be associated in the production of phase I and II enzymes that are essential for metabolism of carcinogen within the physiological system. Phase I enzyme has potential to activate the carcinogen whilst phase II enzyme is responsible for attaching polar group to the activated carcinogen that facilitates its

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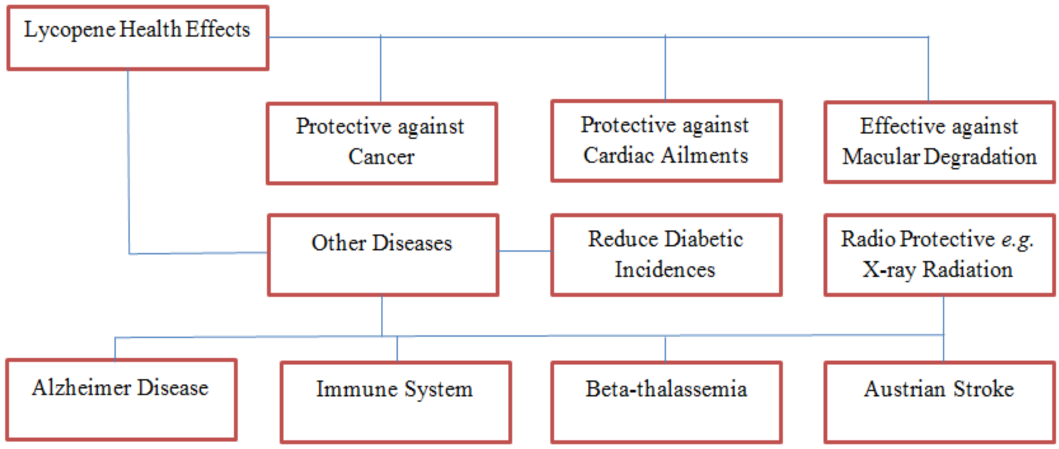


**Figure 3:** Health benefits of lycopene

excretion. Furthermore, it activates antioxidant response element transcription system within the body to inhibit carcinogenesis, mutagenesis and some other forms of toxicity (Linnewiel et al., 2009; Butt et al., 2013).

Lycopene is a viable antioxidant and beyond this property also attributed for its antiproliferative effects against oncological incidences. Its functionality is associated in diminishing the insulin growth factor thus lowering rate of cancer prevalence. Researchers have unified their opinions on inverse association between blood lycopene level and risk of various cancer types. This individualized approach is also supported by mechanistic exploration with different cell cultures and animal models (Fenko et al., 2009). It has direct relation with phase I and II enzymes and also protects cell membrane, DNA and other macromolecules by reactive oxygen species. Furthermore, it is involved in regression of cancer by interrupting cancer cell growth cycle, apoptosis, hormone regulation and carcinogen metabolism (Butt et al., 2013).

Numerous case studies have indicated chemopreventive role of lycopene regarding aerodigestive tract cancers (oral cavity, pharynx, larynx and esophagus). Accordingly, an oncological efficacy trial was carried out on hamster buccal pouch carcinogenesis induced by 7, 12-dimethylbenz anthracene using lipid peroxidation, glutathione reductase and glutathione S-transferase as biomarkers of chemoprevention. After 2 weeks, biochemical measurements revealed modulating effect of lycopene against buccal pouch cancer and enhancing activities of glutathione redox cycle enzymes (Bhuvaneswari et al., 2001). In a similar study, combined effect of lycopene, vitamin C, flavonoids and phytosterols was established in the regression of aerodigestive tract carcinoma (Stefani et al., 2000).

Colorectal cancer is one of most prevalent malignancy related to colon. Many type of tumorogenesis are accelerated by phosphatidylinositol 3-kinase (PI-3K)/Akt pathway that in turn stimulates transcription and protein translation, essential for cell growth, survival and progression. Cumulative evidences suggested that lycopene could suppress proliferation of colon cancer through modulation of PI-3k. For the purpose, concomitant effect of lycopene and eicosapentaenoic acid (EPA) was determined in human subjects. It was observed that combination of lycopene and EPA inhibit cell growth at higher concentration and somehow reduce at low concentration (Tang et al., 2009). Previous studies have reinforced lycopene association with reduced cancer risk. A case study on colorectal cancer explicated that the patients with colorectal adenomas (a type of polyp proved as precursor of colorectal cancer) had significant lower level of lycopene (35 %) as well as β-carotene (25.5 %) compared to healthy adults. Administration of

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lycopene at early stages has ability to slow down cancer cell progression (Slattery et al., 2000).

It has been reported from the research in the Harvard University that the subjects consuming appreciable dosage of lycopene have resistance against various cancer lines especially prostrate (Dahan et al., 2008). An inverse correlation exists between the consumption of high lycopene and prostate cancer as observed through a research intervention. Men with high consumption of lycopene in diet reported 25 % less incidences of prostate cancer and overall 44 % reduced risk of other cancers (Tang, 2009). According to Ansari et al. (2004), lycopene therapy has an effective role in the prevention of hormone refractory metastatic prostate cancer. In current frantic incidences of cancer, lycopene must be administrated at early onset of prostate cancer due to its relative innocuous nature rather than chemotherapy and growth factor inhibitors. Afterwards, Kanagaraj et al. (2007) reviewed lycopene impact on the components of insulin growth factors (IGF); found a significant decrease in the proliferation of cells treated with lycopene.

Carcinomas of breast, ovary and endometrium are hormone dependent and have some biological similarities. Numerous epidemiological studies have presumed that diet and nutrition play a preventive role in progression of hormone related cancer milieu. Chalabi et al. (2004) studied breast cancer lines for BRCA1 and BRCA2 for transcription and translation. According to their findings, lycopene dietary sources have direct relation on oncogenesis and developed nutrigenomic link of lycopene. It was hypothesized that lycopene derivatives may act as ligands and regress tumorogenesis. Likewise, females consuming ample amount of watermelon have five times less likely risk of cervical cancer (Rao et al., 2007; Wu et al., 2007; Moussa et al., 2008). The cascade of events is due to high anti-proliferative properties of lycopene as compared to α- and β-carotene (Levi et al., 2001). Lycopene also hold the ability to control autocrine and paracrine system a contributory factor in the development of the endometrial cancers and malignant tumors (Salman et al., 2007).

### *c. Cardiovascular complications*

Cardiovascular diseases (CVD) is contributed by sedentary lifestyle and reported as a leading cause of mortality. Cardiac risk is elevated due to consumption of high cholesterol diet resulting subacute chronic inflammation. Distinctively, LDL-cholesterol, serum amyloid A (SAA) and inter-cellular adhesion molecule (ICMA-1) are the risk factors thereby facilitate atherosclerosis progression and cardiovascular events (Verschuren et al., 2011).

Hypercholesterolemia is a condition in which serum lipid level increases especially cholesterol and low density lipoproteins (LDL) that further leads to atherosclerosis. Dietary lycopene exert cardio-protective effects due to their high antioxidant activity (Cauza et al., 2004). Apart from lipid lowering drug therapy, dietary interventions are encouraged to attenuate hypercholesterolemia. For the purpose, fifty-six Albino male rats were administrated on tomato lycopene for 10 weeks. The resultant data indicated that the rats fed on hypercholesterolemic diet induced significant increase in serum total lipid level, total cholesterol, low and high density lipoprotein and decreased levels of glutathione peroxidase and malonaldehyde. On the contrary, diet having tomato lycopene mitigated the signs and symptoms of hypercholesterolemia (Basuny et al., 2009). In another research, impact of lycopene was studied on macrophages. The derived results demonstrated that macrophages enrichment with lycopene potentially suppressed cellular cholesterol synthesis and ameliorated macrophages LDL receptor ability. This effect can lead to enhanced clearance of LDL from the plasma thus lycopene is recognized as hypocholesterolemic agent (Fuhrman et al., 1997).

The watermelon is also helpful to lessen some other metabolic syndromes owing to vitamin A, $B_6$, C, magnesium, potassium. These along with lycopene are health promoting functional ingredients associated with reduced risk of cardiovascular disorders. Heart attacks, ischemic strokes and atherosclerosis are faced through the oxidation of low density lipoprotein and their curing has been observed though high consumption of lycopene (Omoni and Aluko, 2005). High intake of lycopene lowered the thickness of the internal layer of the blood vessels thus reducing the risk of myocardial infarction (Zhang and Hamauzu, 2004). Consumption of watermelon is more advantageous as lycopene is readily available through watermelon (Rao and Agarwal, 1999; Weisburger, 2002).

***d. Diabetes mellitus***

Numerous experimental studies and surveys have indicated that patients with hyperglycemia are more prone towards the risk of coronary complications. In this context, elevated oxidative stress and LDL oxidation are the major contributory factors. High glycemic diet significantly elevates glucose and its auto-oxidation consequently generates free radicals and cell damage (Micol et al., 2007). Besides, Sugiura et al. (2006) explored phenolics *i.e.* lycopene, lutein, β-carotene, β-cryptoxanthin and β-carotene for their hypoglycemic action. The upshots of the research showed an inverse association of carotenoids with serum aminotransferases in hyperglycemic subjects. Among all, lycopene is proved as deterrent constituent against serum aminotransferases and significantly prevents the onset of hyperglycemia. Additionally, oxidative stress is increased during hyperglycemia phase through intracellular reactive oxygen species (ROS). As a result of this imbalance inside the cell ROS damages the mitochondria, DNA, lipids and other organelles leading to apoptosis. Investigation of Micol et al. (2007) also proved hypoglycemic perspectives of lycopene and elucidated that watermelon lycopene extract significantly improves lipid and glycemic metabolism.

Recent research studies have marked obesity and diabetes as the major public health problems in most of the countries. The diabetes prevalence is so high and estimated that its level raised from 135 to 300 million by the years 1995 to 2025 (American Diabetes Association, 2007). During the progression of obesity, adipokines (cytokines and chimiokines) are synthesized that play an important role in general body physiology. Massive development of adipose tissue leads to inflammation resulting from the excessive production of chimiokines and cytokines thus leading to type II diabetes. Lycopene is a lipophilic carotenoid stored in adipose tissues thereby reduces the pathologies linked with obesity and hyperglycemic conditions (Madhava et al., 2011).

The lycopene based functional drinks have potential to reduce malignant transformation of oxidized cholesterol in diabetic state. The lycopene decreases diabetes in linear fashion by managing glucose abnormalities. Lycopene owes ability to decrease body glucose and raise insulin level in type II diabetes. In an investigation, Jian et al. (2008) studied the impact of oral supplementation of lycopene in normal rats for twenty eight days. The lycopene was daily supplied in doses as 0, 200, 500 and 2000 mg/kg body weight by gavage. No significant signs of abnormality were noticed for hematology, urinalysis and organs weight. However, a decline in glucose value was observed at higher lycopene dose. The significant differences in body glucose were noted between control and lycopene treated rats i.e. 205.6 ± 44.3 and 132.1 ± 35.9 mg/dL, respectively. Conclusively, they confirmed lycopene as an ameliorating factor for hyperglycemia.

Alongside, substantial studies have revealed negative association of hyperglycemia with the central nervous system (CNS), leads to cognitive dysfunction. High intracellular glucose level induces learning and memory impairments and neurochemical and structural abnormalities. In a rat modeling, provision of lycopene supplemented diet ameliorates cholinergic dysfunction, cognitive deficit nitric oxide and reduces oxidative stress. Moreover, a marked decline in serum glucose level was observed i.e. 5 % after 4 mg/day supplementation of lycopene (Kuhad et al., 2008). Clinical findings also delineated lycopene a good option for the development of functional foods owing to its hypoglycemic perspectives. In this context, Mellert et al. (2002) conducted a thirteen days study on normal wistar rats to judge the lycopene response. They deduced that lycopene interim supplementation significantly reduces body glucose level i.e. 13 %.

Watermelon extract is considered as a concentrated source of nutrients along with lycopene. In a trial, 1 % extract was administered to the diabetic rats. At the termination of study, rise in insulin level 37 % whilst decline in glucose 33 % were observed. The study indicated watermelon extract as a hyperinsulinemic and hypoglycemic product (Ahn et al., 2011). In a nested case control trial, data were collected for diabetic middle aged women from a period of 1992 to 2003 to find out the association of dietary lycopene intake with insulin level. During ten years of follow up, observed cases depicted a linear correlation between lycopene and insulin level and a rise of 37-45 % was noticed. The wide range of variations was attributed to the altered body metabolism of diabetic patients. The findings reflected lycopene ability to improve insulin sensitivity and glucose metabolism (Wang et al., 2006).

There are some convincing epidemiological evidences in favor of lycopene, vitamin E and vitamin C with decreased incidence of cardiovascular complications in diabetic patients. Accordingly, a study was conducted by Upritchard et al. (2000) to determine the effect of lycopene and vitamin E and C on LDL oxidation and inflammatory activity in type II diabetes. Initially, 57 diabetic patients received functional juice as a source of dietary lycopene (500 mL/day) along with vitamin E (800 U/day) and vitamin C (500 mg/day). The results indicated that high intake of lycopene and vitamin C and E are one of the options to reduce various coronary complications in diabetic patients. Likewise, lycopene dose dependent effect was estimated in streptozotocin (STZ) induced hyperglycemic rats to find its potential against hyperglycemia, hyperlipidemia and abnormal antioxidant status. Furthermore, results were compared with hyperglycemic and normoglycemic rat groups. A dose dependent decrease in glucose level and TBAR along with rise in insulin value was noticed. The investigation elucidated antidiabetic activity of lycopene by lowering free radicals (Ali and Agha, 2009).

Diabetes based neuronal abnormalities are attributed to the high intracellular glucose. Effect of lycopene was determined with special reference to its antioxidative and anti-inflammatory behavior on oxidative stress, cognitive function and inflammation in streptozotocin (STZ) induced diabetic rats. During the ailment, acetyl cholinesterase activity, a biomarker of cholinergic dysfunction increased in cerebral cortex of diabetic rats about 1.8 fold. Moreover, a rise in thiobarbituric acid reactive substances was about 2 folds. It was concluded that lycopene has ability to mitigate cognitive deficit, inflammation and oxidative stress in diabetic rats (Kuhad et al., 2008).

Hyperalgesia is a neuropathic pain in diabetes because of microvascular complications. An investigation performed by Kuhad et al. (2008) has revealed the therapeutic role of watermelon lycopene against neuropathic pain associated with diabetes. Additionally, lycopene has ability to reverse the hyperalgesic stage to some extent. Similarly, role of lycopene as an antioxidant was assessed in streptozotocin (STZ) induced diabetic rats, In this regard, 6 female rats received 10 mg/kg body weight lycopene once a day for three weeks. Diabetes induction caused significant rise in serum glucose and reduction in body weight. However, lycopene showed assuaging effect on diabetic rats by reducing serum glucose level up to 25 %. Weight loss was also prevented after two weeks of lycopene administration. Conclusively, lycopene supplementation proved valuable to combat against hyperglycemia (Duzguner et al., 2008).

***e. Macular diseases***

Macular degenerative disease onsets with the thinning of macula layer of retina thereby resulting in gradual decrease in vision. The symptoms include appearance of yellow spots (Bramley, 2000). There are two types of age related macular degeneration (AMD) including wet and dry. However, dry AMD is more prevalent further in turns to wet AMD when new blood vessels develop to reduce the dryness of macular layer. The development of such vessels favors hemorrhage, swelling, and scar on the eye tissue (Bazzano *et al*., 2002). The utilization of carotenoids or their rich sources can reduce the risk of macular and other degenerative disorders. In an experimental study of macula-degeneration, subjects with low lycopene-serum concentrations were at high risk. Lycopene is also effective against immunodeficiency diseases like HIV and cerebral damage microangiopathy in Austrian stroke (Kun et al., 2006).

## CONCLUSIONS

Watermelon is a proven distinctive source of lycopene claiming new era vitamin due to health promising properties. Diversified nature of watermelon lycopene has attained core attention of researchers in terms of bioavailability and absorption. Safe and sound extraction procedure with minimal loss is desirable at industrial scale. Finally, available information from numerous cell culture and animal models have illuminated the therapeutic role of lycopene against life threatening metabolic syndromes like oxidative stress, cancer, CVD, diabetes etc. Nevertheless, still there is a need for dietary intervention for better understanding of role of lycopene on human health.

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