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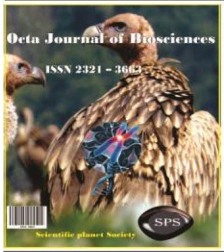

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Lycopene- Sources, Extraction, Nutritional and Medicinal value: A review

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ABSTRACT
Dietary lycopene is a caretenoid found in red and yellow fruits and vegetables majorly in tomatoes. The most thermodynamically stable form of all trance lycopene is present in tomatoes but it is less bioavailable then sis isomers of lycopene. Tomatoes contribute to about 85% of dietary lycopene intake. Lycopene is known for its antioxidant properties and it scavenging properties against oxygen free radicals and oxygen active compounds. It prevents Biomolecules like DNA, lipids and proteins from oxidative damage. Researches strongly suggest that lycopene plays an important role in reducing the risk of various types of cancer including pancreatic, colorectal, cervical and stomach cancers. Therefore it can be used as functional food and also for Pharmaceutical purposes.
Keywords: Lycopene, Free radical scavenging, Essential Nutrient

1. INTRODUCTION
Lycopene is a predominating pigment found fruit and fruit vegetables like red and pink flesh tomatoes, papaya, watermelon guava and Brazilian fruit pitanga. It is one of the most commonly encountered bioactive acyclic carotene. (Amaya et al., 2008). It is a light gathering at soluble pigment which protects against toxic effects of Oxygen and light. Lycopene is a cyclic and is symmetrically planar with no vitamin A activity. It is one of the 600 caretenoid found in nature and was first isolated by Willstatter and Escher in 1910. This hydrocarbon caretenoid is also a major component found in blood serum and has been extensively studied not only because of the colour it imparts but also the the antioxidant and anticarcinogenic properties associated with it. The all-trans- isomer of lycopene present in red tomato has been found to prevent heart attacks, stroke and several types of cancers in humans by reducing platelet accumulation in the body.

The inability of body to synthesize lycopene makes an essential component required in our diet. Being natural is synthesized in plants and animals, they are an important source of lycopene 85% of which comes from tomato and tomato based product alone and the rest from other red colored fruits and vegetables (Bohm *et al*., 2001; Nguyen and Schwartz 1999). In tomato the outer part of the pericarp of chromoplast contains crystalloids which are thin sheets of lycopene and are biosynthesized mainly during ripening process. (Kirk and Tilney-Basset, 1978).

The singlet-oxygen-quenching ability of lycopene makes it one of the most powerful natural antioxidant as it is higher than beta carotene and Alpha tocopherol by 2 and 10 times respectively. Even with a. little knowledge of its biochemical mechanisms, lycopene is said to prevent the oxidative damage to DNA, protein and lipids and also shows resistance to bacterial infections.

Lycopene along with other caretenoid can be degraded by many physical and chemical factors like high temperature, extreme pH and exposure to light (Crouzet and Kanasawud, 1992). Processing factors light thermal heat treatment at or above 100 degree Celsius in presence of Oxygen and light, canning and freezing result in degradation of lycopene (Cano *et al*., 1996).

Following work aims to review the sources, availability and nutritional properties of lycopene in order to understand the beneficial pigment and gain knowledge about the use and importance of the red food pigment lycopene in the field of food and nutrition, medicines and biochemistry. The paper reviews Sources of lycopene nutritional and medicinal value of lycopene and how it affects various diseases that can be life threatening to humans.

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2. Sources of lycopene

Ability of human body to synthesize keratin oil made it an essential nutrient that should be present in our diet. Red colour fruits and vegetables are a source of lycopene in our diet and a source among them being tomato in both Raw and processed form it is involved majorly in food habit inform of sauces, jam, ketchup ,soup, powder forms etc. thus it makes up to 85% of lycopene consumed by body. Raw tomato can provide 3100 microgram lycopene per hundred grams. The amount of lycopene in tomato is greatly affected by its variety ripeness climate geography processing techniques. It is also found in two forms into metre which areglobulus and sheet form (Laval-Martin, 1974). Daily intake take of lycopene is recommended to be 25 mg per day. Porrini *et al.*, 1998 reported that the thermodynamically stable all-trans form of lycopene is present in Raw tomatoes in very high quantity (94 to 96%) whereas at least 50% cis-isomers are present in human plasma and tissues with 5-cis-, 9-cis-, 13-cis-, and 15-cis-lycopene being the most common ones. Different sources of lycopene are mentioned in Table 2.1

2.1 Lycopene from microbial sources

Y. lipolytica is used for production of lycopene. Due to its inability to produce lycopene naturally, two genes namely phytoene synthase and phytoene desaturase are introduced in it but the amount of lycopene that can be produced is still not properly known. Still the property of *Y. lipolytica* to grow on simple substrates and produce high biomass like raw glycerol has encouraged its use in the production of commercial lycopene. Being non pathogenic yeast it can be used for food and Pharmaceutical purposes. Furthermore the east can store good amount of hydrophobic compounds as it produces lipid bodies. This bodies are also responsible for storage of lycopene in the yeast cell.(Matthä *et al.*, 2014).

Escherichia coli and *Saccharomyces cerevisiae* are also used for lycopene production and among the above two the later is safer host but the production of lycopene is more by *E coli*. (Chen *et al*., 2016**)** conducted a study in which they constructed lycopene biosynthesis pathway by integration of CrtE, CrtB and CrtI gene in *S. cerevisiae CEN.PK2*. The study reported 22 fold increase in lycopene production by *S. cerevisiae* through combining host engineering with pathway engineering.

Blakeslea trispora, and *E. coli* are used for lycopene production but threaten food safety issues as they require addition of cyclase inhibitors and produce endotoxins respectively (Ray and Raetz, 1987). *Escherichia coli* with the help of metabolic engineering produces a precursor of lycopene and has higher yield than tomato (Deng and Liu, 2016).

Blakeslea trispora is used to produce high quality lycopeneand is seen as it's ideal source found in nature Wang *et al.,* (2014) in their study reported that the lycopene produced by *B. trispora* has higher nutritional quality and content than tomatoes. The mutant C9 strain of *Phycomyces blakesleeanus* accumulates lycopene (Guardia *et al*., 1971).

3. Extraction and isolation of lycopene

Montesano *et al*., (2008) in their paper gave an innovative method for extraction of high quality lycopene from tomato powder. This method recovers lycopene in its all *Trans* configuration as it is present in tomato naturally. The process was carried out in subdued lighting. Fig 3.1 depicts the procedure for extraction

Raw tomato
↓
Slicing (1.5 cm cubes)
↓
Mincing in high speed mills (<4mm chunks)
↓
Dilution with deionizer water (1:1 w/v)
↓
Blending in waring blender
↓
Boiling (10 min.)
↓
Extraction-Naviglio Extractor (8 Bar pressure, 5 min, 50% moisture)
↓
Vacuum filtration (16% moisture)
↓
High speed blending with Acetone (1:1 w/v) and vacuum filtration (done 3 times within 45 sec.)
↓
Diethyl ether (1:1 w/v) added to solid residue and vacuum filtered (done 3 times 30 sec. each)
↓
Absorption on filter paper to remove oil from tomato seeds(3 times, -15°C in darkness)
↓
Nitrogen flow (10 min.)
↓
Lyophylisation (2hrs.)
↓
Storage (-20°C)

Fig 1: Extraction of Lycopene from Tomato

Metkar et al., (2014) in his paper *"Studies on extraction, isolation and application of lycopene"* presents various methods that can be used to extract and isolate lycopene from various tomato products.

Tomato paste (50gms.)
↓
Dehydration by adding 65ml methanol
↓
Vigorous shaking
↓
Storage for 2 hrs.
↓
Filtration the suspension
↓
Addition of 75 ml of 1:1 mixture of methanol and carbon tetrachloride and mixing for 15 min
↓
Addition of one volume of water
↓
Phase separation by separating funnel
↓
Evaporation of carbon tetrachloride
↓
Dilution of residue using 2ml of benzene
↓
Crystallization by addition of 1ml of boiling methanol followed by ice bath
↓
Washing of crystals by boiling method using benzene (10 times)

Fig 2: Extraction of Lycopene from Tomato Sources

The extraction of lycopene from *Saccharomyces cerevisiae* was performed by Bahieldin *et al*.,(2014). The strain was developed by them by over expressing the synthetic genes *ctrE*, *ctrB* and *ctrL* of *Erwinia uredovora*.The following procedure was used by them to harvest the cells and extract lycopene from them.

Harvesting of *S. cerevisiae* cells by the process of centrifugation (3000xg for 10 min.)
↓
washing with distilled water
↓
lyophilization and storage at -80°C till use
↓
Suspension of 100mg of lyophilized cells in 2ml of 0.9 M sorbitol solution
↓
Addition of glass beads (0.4 mm dia.) and 10 ml of acetone
↓
Pulverization of cells to collect the acetone fraction
↓
Extraction of lycopene by addition of 10 ml of petroleum ether
↓
Evaporation till dry

Fig 3: Extraction of Lycopene from *Saccharomyces cerevisiae*

In a similar research done by Yamano et al., (1993) on production of lycopene from *S. cerevisiae* a method similar to the above mentioned was used.

- Suspension of 100mg of lyophilized cells in 15ml acetone and 20g of glass beads followed by pulverization of cells (done 4 times)
- Evaporation of the resulting extract to dryness

Production of lycopene from *Candida utilis* which was performed by Miura et al., (1998) is yet another research that uses similar method for lycopene extraction.

A different method was used by Matthau F., et. al. (2014) to extract lycopene from *Yarroeia lipolytica.*

Suspension of 300mg of in 20ml of 10M phosphate buffer (pH 7)
↓
Centrifugation (1500xg for 5min)
↓
Addition of 10ml of phosphate buffer in the supernatant
↓
Centrifugation (100,000xg for 1hr)
↓
Extraction of each phase 3 times with the help of solvent
↓
Evaporation to desired volume to obtain lycopene

Fig 4: Extraction of Lycopene from *Yarroeia lipolytica.*

4. Bioavailability and Metabolism

Tomato puree and sauce are more bioavailable then raw tomato. According to Rao and Agarwal 1999, the bioavailability of lycopene increases when all-trans lycopene is isomerized into cis confirmation by heat. Various factors affect the absorption of lycopene in the body. Factors like fat intake, fibre, fat substitute, plant sterols,cholesterol reducing drugs and the body is health state effect amount of lycopene absorbed by the body. The amount of fat intake positively affects the lycopene absorption by the body by inducing bile acid which supports the absorption of lycopene in the mucosal lining of the intestine. Along with this, the presence of Beta carotene also has a positive effect in lycopene bioavailability (Johnson et al., 1997**)**. According to (Reddy, 1995) in India 5 to 10 grams of fat should be included in diet per day proper absorption of lycopene. On contrary to this fat substitutes negatively affect update of lycopene by binding it and creating hydrophobic sink in the lumen in small intestine. Similar effect is shown by plant sterols and cholesterol reducing drugs.

The orange coloured variety of tomato known as Tangerine lacks the enzyme caretenoid isomerase. This causes prolycopene (tetra-cis-lycopene) to be the predominant lycopene in Tangerine variety of tomatoes and is also responsible for the orange colour. This presence makes this variety more bioavailable than the red tomatoes as the cis isomers are more bioavailable compared to all-trans isomers. The study conducted by (Ishida et al., 2005) show that the plasma lycopene responses higher during consumption of Tangerine sauce than that of red tomato sauce.

lycopene is transported in the body by passive diffusion in the brush border of mucosal cells and is converted into oxydative lycopene by enzyme β-carotene-15,15\dioxy-genase and then it is present in blood serum.(Olson, 1961). Lycopene exits the mucosal cells in form of chylomicrons. Passive transfer is also done buy several tissues, kidney, adipose, lungs and reproductive organs to take up lycopene. Little is known about the transportation of lycopene in the body and is said to be done by specific proteins or by fat globules (Gugget and Erdman, 1996).

5. Medicinal Importance

The disease modulating process biological activity mechanism of caretenoid is still unknown but a variety of studies support the anticarcinogenic properties of lycopene and suggest various reasons for this. Some of them being the antioxidant action of lycopene, the property of lycopene to increase cell-cell communication, reduce mutagenesis, induce tumor cell proliferation and increase antitumor immune responses (Clinton, 1998). Being one of the most potent antioxidant due to its singlet-oxygen-quenching ability, handmade lycopene an interesting cancer preventive agent. Evidences suggest that it acts as a micronutrient and provides protection against broad range of cancer, heart disease and other free radical induced degenerative diseases. (Kun et al., 2006).

Erhardt et al., (2003), conducted a research and found that patient with colorectal cancer had low levels of lycopene in blood serum, 35% lower than the normal patients and suggested that low levels of lycopene in blood serum increased the chances of colorectal adenomas which is a precursor of colorectal cancer.

According to the research of (Miller et al., 1996**;** Rao et al., 2003**)** among the caretenoid lycopene is one of the most potent free radical scavenging agent due to the large number of double bonds present in its structure. Reaction of caretenoid with oxygen free radicals results in the caretenoid turning into excited triplet state along with dissipation of heat. Caretenoid in this form can further participate in free radical scavenging reactions and the number of double bonds in the structure is directly proportional to the efficiency of the scavenging process. Along with oxygen free radicals the lycopene also interacts with hydrogen peroxide and nitrogen dioxide which are reactive oxygen species (Bohm et al., 1995). It inhibits ploriferation of tumor cell lines and decreases the chances of mammary tumors. A study by (Giovannucci et al., 1995) suggested that high intake of dietary lycopene decreased the chances of prostate cancer. Another study by (Clinton, 1999) reported that lower risk of prostate carcinoma was seen in men with higher concentration of blood lycopene. Further studies this matter showed that high intake of lycopene prevented many forms of cancer including cervical, colon, rectal, stomach oesophagal cancer.Research works by (Etminan et al., 2004 ; Boileau et al., 2003) reported the effectiveness on lycopene in preventing prostate cancer.

(Nkondjock et al., 2005) conducted three year research to study the effect of lycopene on pancreatic cancer and identified the mechanism by which lycopene prevent the cancer. It was reported that lycopene activated and increased the production of cancer preventing phase II enzymes NAD(P)H: quinone oxidoreductase (NQ01) and glutamylcysteine synthetase (GCS) by expressing a reporter gene called luciferase.

Epidermiological studies suggest that lycopene provide cardiovascular benefits by preventing oxidative damage to DNA and other low density lipoproteins (Ojima et al., 1993). A study conducted on 39876 middle-aged and older women for 7 years concluded that intake of dietary lycopene greatly reduced the risk of CVD in them. Another 3 week long study on 12 healthy women reported that the consumption of 8 mg lycopene per day and redused the risk of free radical oxidation of LDL cholesterol in the body and thus prevented atherosclerotic plaque formation which is one of the major risk factor in cardiovascular diseases.(Visioli et al., 2003)**.** Further low level of circulating lycopene in blood increased the risk of myocardial infection and an increased risk of death from coronary artery disease (Kristenson *et al.*, 1997).

6. CONCLUSIONS

A potential chemopreventive agent, lycopene is a predominant caretenoid found in human liver,prostate, adipose tissue and testis. It protects the cell from oxidative damage by oxygen free radicals and also other reactive oxygen species. An integral part of the diet due to its presence in tomato and other red and Orange fruits and vegetables, lycopene also acts as a micronutrient.

The intramucosal processing of lycopene is not very well known. Similarly little is known about the mechanism involved in formation of lycopene that is present in human serum. However studies strictly suggest that high amount of lycopene content in diet reduces the risk of of several types of cancers and cardiovascular diseases due to its free radical scavenging properties. Hence further research is required to properly understand the disease preventing mechanism of lycopene and its role in various other functions performed by the body.

Table 2.1: Sources of lycopene

Food Source	Amount(mg/100gm wet weight) (Singh and Goyal, 2008)	Amount (mg/100g wet basis) (Basuny, 2012).	Amount (microg/g wet basis) (Amin *et al.*, 2009)
Tomatoes Red	3.1-7.44	0.72 – 20	8.8 - 42
Watermelon	4.10	2.30 – 7.20	23 - 72
Tomato Juice	7.83	5.00 – 11.60	86 - 100
Tomato soup	3.99	7.99	63 - 131
Tomato paste	30.07	5.40 – 15.00	124
papaya	2.0-5.30	0.11 – 5.30	20 - 53
Guava	5.40	5.23 – 5.50	54

Table 2.2: Lycopene production yield by different micro-organisms

Escherichia coli	16 mg/g	(Matthä *et al.*, 2014)
Saccharomyces cerevisiae	2.43 mg/g	(Chen *et al.*, 2016)
Modified *Saccharomyces cerevisiae*	54.63-55.56 mg/g	(Chen *et al.*, 2016)
Y. lipolytica	16 mg/g	(Matthä *et al.*, 2014)
Blakeslea Trispora	0.9448 mg/g (4%glucose, 1% sunflower oil)	(Sevgili and Erkmen, 2019)
Phycomyces	15 mg/g	(Guardia *et al.*, 1971)

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