Biomedicine & Pharmacotherapy 129 (2020) 110459

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Review

Potential inhibitory effect of lycopene on prostate cancer

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ARTICLE INFO

Keywords:
Lycopene
Prostate cancer
Anti-Cancer effect
In-Vitro and *in-vivo*study

ABSTRACT

Studying prostate cancer is important due to its high annual incidences and mortality rates in the world. Although prostate cancer mortality rates are reduced using new therapy, complicated routes and side effects of these current drugs require a daily available treatment for prevention. Lycopene is a natural, prominent, and effective product which has a high value in diet. The anti-cancer effect, non-toxicity, safety and preventive or therapeutic roles of lycopene have been investigated in several studies. In the current review, we have collected information about the anti-cancer, anti-progressive and apoptotic effects of lycopene on prostate cancer. This article is a summary of the most important original and review articles on lycopene and its anticancer effects that are systematically categorized and presents information about the molecular structure, different sources, biological functions, and its *in-vivo* and *in-vitro* effects of lycopene on variety of cancerous and normal cells. The clinical studies provide a clear image for continuous use of this adjunctive dietary for different type of cancers, especially prostate cancer in men. In addition, this article discusses the various molecular pathways activated by lycopene that eventually prevent or suppress cancer. Lycopene has been found to effectively suppress the progression and proliferation, arrest in-cell cycle, and induce apoptosis of prostate cancer cells in both *in-vivo* and *in-vitro* conditions. Additionally, lycopene showed that it could modulate the signaling pathways and their protein for the treatment or prevention of prostate cancer.

1. Introduction

Lycopene, as a main dietary antioxidant, belongs to the carotenoid family, and it is synthesized and found in red and yellow fruits or plants [1]. Predominantly, it exists in carrots, watermelons, papayas, gac fruit (red), asparagus, and (yellow) parsley. Structurally, lycopene (with the

Abbreviations: GJC, Gap Junctional Communication; Hl-60, Human promyelocytic leukemia cell line; NF-κB, Nuclear Factor-κB; JNK, c-Jun N-terminal kinase; Nrf2, Nuclear factor erythroid 2-related factor 2; BDNF, Brain-derived neuro trophic factor; iNOS, Inducible Nitric Oxide synthase; COX-2, Cyclooxygenase-2; PGE2, Prostaglandin E2; NO, Nitric Oxide; IL-1β, Interleukin 1 beta; IL-6, Interleukin 6; TNF-α, Tumor necrosis factor alpha; ROS, Reactive oxygen species; Rb, Retinoblastoma protein; p53, Tumor protein p53; PrEC, Prostate epithelial cells; IGF-1, Insulin-Like Growth Factor 1; HT-29, cells Human Colorectal Adenocarcinoma cells; MMP-7, Matrix metalloproteinase-7; GSK-3β, Glycogen synthase kinase-3β; Akt, Protein kinase B; ERK1/2, Extracellular signal-regulated protein kinases 1 and 2; PI3K, phosphatidylinositol-3-Kinase; MAPK, mitogen-activated protein kinase; AP-1, Activator protein-1; PC3, Prostate cancer cells; miR, let-7f1 microRNA Lethal-7; ACTH, Adrenocorticotropic hormone; BMI, Body mass index; Skp2, S-phase kinase-associated protein 2; PSA, Prostate specific antigen; STEAP, Six-transmembrane epithelial antigen of the prostate; BRCA1, Breast cancer gene 1; BRCA2, Breast cancer gene 2; CaP, Cancer of prostate; PEC, Prostate epithelial cancer; LNCap, Lymph Node Carcinoma of the Prostate; VeCaP, Androgen–independent prostate cancer cell line; Bax, BCL2-Associated X Protein; BCL2, B-cell lymphoma 2; BCO2, β-carotene-9′10′-oxygenase 2; PPARγ, Peroxisome Proliferator Activated Receptor; LXRα, Liver X receptor α; ABCA1, ATP-binding cassette transporter 1; PC-3MM2, metastatic hormone refractory subline of PC-3; PBH, Benign prostate hyperplasia; HRPC, Hormone-Refractory Prostate Cancer; HGPIN, High-grade prostatic intraepithelial neoplasia; TRAMP, TRansgenic Adenocarcinoma Mouse Prostate; IGFBP-3, Insulin-like growth factor binding protein 3; uPAR, Urokinase-Type Plasminogen Activator Receptor; c-fos, Proto-oncogene and homolog of the retroviral oncogene v-fos

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https://doi.org/10.1016/j.biopha.2020.110459
Received 21 May 2020; Received in revised form 13 June 2020; Accepted 23 June 2020

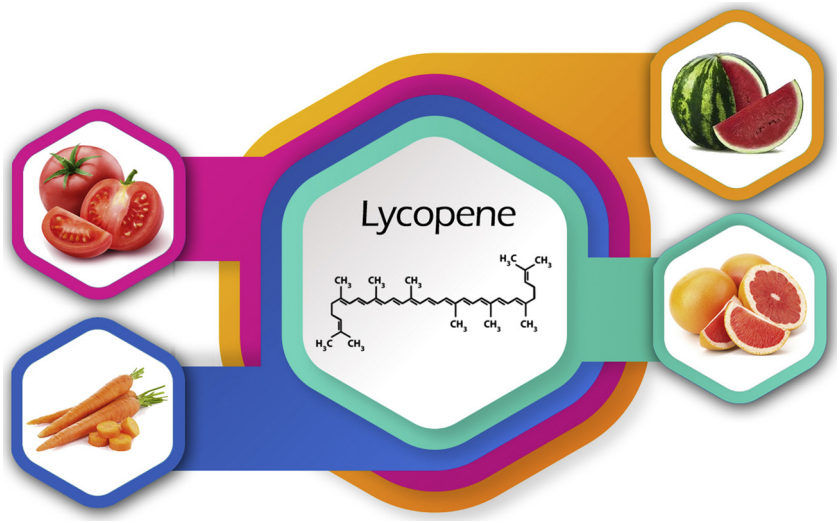

Fig. 1. Source and structure of lycopene.

chemical formula of $C_{40}H_{56}$), is a tetra-terpene lipophilic, along with conjugated double bonds (Red color factor), and the structure of lycopene in plants is all-trans isomer [2] (Fig. 1).

Because of the lipophilic properties of lycopene, it shows poor bioavailability, and the main source of lycopene in diet is all-trans isomer. On the other hand, in the body (blood, fluid and tissues) dominant of lycopene is cis-isomer, which more is soluble in water and more bioavailable. Therefore, this isomer could enter the blood by better adsorption through the tracts compared to all-trans form. In fact, in *in-vitro* conditions, altering trans isomer to cis-isomer can be occurred, by heating the lycopene in nutrition sources (i.e., tomato paste), and in *in-vivo* conditions trans to cis isomerization is done using gastrointestinal and liver enzymes [3–5].

Its natural form (trans-isomer) and metabolized form (cis- isomer) in *in-vitro* and *in-vivo* environments. In phase 1, physiological pharmacokinetic model for three different doses of lycopene was used in a healthy person, during determining period, and the results showed that the adsorption of lycopene with a 10 mg dose, was greater in comparison with other high doses (30 and 50 mg). Moreover, the study showed that most of the people absorbed 6 mg of lycopene. It is important to understand the proper pharmacokinetic dosage of lycopene needed for controlling cancer [6]. Another animal study, described measuring the absorption of tissues and pharmacokinetics of lycopene, and showed that the liver, adrenal glands, spleen, intestinal tissues, and lymph nodes received the highest concentration of lycopene. The concentration of lycopene, in 1 and 5 days after receiving the last dose, were 66 and 91 nmol/g in the liver, while the concentrations of lycopene were less than 0.2 nmol/g in prostate, in both times [7].

Dietary and synthetic lycopene safety was evaluated in different humans and animals, and *in-vitro* studies were done for toxicity, genotoxicity, reproductive side effects, liver uptake, metabolism, adsorption and distribution. Evidences in human and animal studies have not reported any side effects of lycopene, in fact, 3 g/kg/d consumption of both forms of lycopene was normal and have not had any unwanted side effects, therefore determining the upper limitation for lycopene uptake, is not necessary [8]. The daily average uptake for lycopene is $0.5-5$ mg/day, but the high consumption of vegetables (i.e. tomato) and fruits could increase the intake of lycopene up to 20 mg/day or more [9].

During the study, it was observed that most of the research conducted to investigate the effects of lycopene was performed, using products which lycopene content was between 10 and 20 %. However, in some newer methods of producing lycopene extraction, purity above 30 % has also been observed. Currently, in the pharmaceutical market, products in the form of tablets, softgels or capsules containing lycopene with amounts of 5–30 mg of active ingredient are available [10].

Pharmacological effects of lycopene were proved as a natural or formulated component in both traditional and new medicines. Many studies showed the remedy effects of lycopene which are along with reduction in inflammation and the risk of chronic diseases. Lycopene can effectively help in preventing and treating cardiovascular diseases and cancers. The level of lycopene in serums and tissue significantly acts as a preventive factor in decreasing the risk of lung and prostate cancers [11]. Several functions of lycopene including anti-inflammatory, anti-oxidative, and anti-proliferative are preventive or curative for heart failures, neoplasms, and cancers. Therapeutic and protective effects of lycopene by inhibition of oxidative stress, neuronal apoptosis and inflammation, and restoration of mitochondrial functions, have been shown in central nervous system disorders or diseases such as; Parkinson's, Huntington's, Alzheimer's, epilepsy and depression as well as efficiency in keeping the memory capacity of rodents [12,13].

Increasing the expression of connexin gene, which is positively related to GJC (Gap Junctional Communication), leads to the reduction in cancer cell proliferation. Recognizing the lycopene's mechanisms is important and necessary for better understanding the effects of lycopene in the treatments and prevention of chronic diseases. In regard with the antioxidant property, lycopene could decrease mutagenesis by trapping free radicals; also, normal concentration of lycopene in the body can stop the growth of cancer cells through inducing apoptosis of cancer cells (i.e. prostate cancer) and by the effect on signaling of growth factor receptor and inhibition of cell cycle progression. Lycopene is also able to interact with other compounds; lycopene in combination with lutein, acts as an antioxidant, moreover low lycopene concentration with the active form of vitamin D3 in Hl-60 (human promyelocytic leukemia cell line), affect cell diffraction and cell cycle progression. Lycopene also shows its function by affecting the signaling pathways, by inhibiting or activating down-stream signaling proteins. For example, the neuro-protective effect of lycopene, mediates the signaling pathways, by inhibiting NF-κB (nuclear factor-κB) and JNK protein (c-Jun N-terminal kinase), and activating Nrf2 (Nuclear factor erythroid 2-related factor 2) and BDNF (brain-derived neuro trophic factor) signaling, as well as keeping homeostasis by restoring intracellular Ca^{2+} [11,12,14]. The main purpose of this article is to highlight the relative importance of lycopene as one of the most powerful and natural antioxidants, and its role in preventing prostate cancer. In this regard, we have reviewed the most prominent researches to investigate the anti-tumor effects of lycopene, in order to show the potential of this antioxidant as well as to investigating its anti-cancer

mechanisms. This article will begin with a review on the molecular structure of this plant-compound and its sources of access, and examining its in-vitro effects and anti-inflammatory actions and mechanisms on signaling pathways in prostate cancer, to provide a sketch of a comprehensive picture for the potential of this substance. Also, a variety of *in-vitro* and *in-vivo* experiments conducted for this anti-oxidant's effects on prostate cancer cells or prostate cancer patients.

2. Anti-inflammatory and anti-oxidative effects

In patients with cancer, chronic inflammation is directly related to tumor relapse and more side effects of surgical and medical treatments. The effects of lycopene on SW 480 human colorectal cancer cells and mice models of xenografts prostate cancer, have shown that lycopene could decrease inflammation in these cells through significant reduction of iNOS (inducible Nitric Oxide synthase), COX-2 (cyclooxygenase-2), PGE2 (prostaglandin E2), NO (nitric oxide), IL-1β (interleukin 1 beta), IL-6 (Interleukin 6), and TNF-α (Tumor necrosis factor alpha), and also lycopene suppresses the activation of NF-κB and JNK and subsequently reduces inflammation [15–17]. Lycopene has shown an anti-oxidative manner in combination with Vit-D and Vit-A or alone [18,19]. Producing some anti-oxidative enzyme (i.e.; catalase, superoxide, dismutase, etc.) regulated by lycopene, also promote the bioavailability of NO that leads to the reduction of mitochondrial, DNA, protein and lipids damage in cells. Lycopene protects cells and endothelium from damage by inhibiting the reactivation of nitrogen and oxygen radicals [2,19,20]. Intravenous injection of lycopene in mice models showed that injected lycopene leads to inhibition of ROS (reactive oxygen species) production and accumulation, and also suppresses related signaling pathways (JNK) [21].

3. Anti-cancer mechanisms

Several *in-vitro* and *in-vivo* studies have shown the roles of lycopene as a preventive factor in fighting against the formation or development of human cancers, such as prostate, lung and breast cancers. Experimental and animal model studies have shown that the concentration of lycopene in serums and tissues could inhibit the growth of cancer cells in different organs and decrease their carcinogenesis. In addition, in regard the anti-inflammatory and antioxidant roles of lycopene, it can prevent cancer through some direct mechanisms, including modulating signaling, arresting cell cycles, inducting apoptosis and changing some enzymes and antioxidants, therefore these properties enable lycopene to prevent metastasis, invasion and angiogenesis of various cancer cells [22–24]. Lycopene suppresses the carcinogen effects on phosphorylation of Rb (retinoblastoma protein) and p53 (Tumor protein p53) proteins, and arrests the cell cycle by inhibiting the expression of cyclin D1 in the G0/G1 phases [25]. In *in-vitro* studies, lycopene could inhibit the growth of normal human PrEC (prostate epithelial cells) in cell culture medium, and also have an effect on the cell junction between cancer cells [25]. The high concentration of IGF-1 (Insulin-Like Growth Factor 1) in serums is related to prostate and breast cancers, and lycopene is able to decrease the progression of the cell cycles, by interfering with mitogenic pathways of IGF-1 [14,26,27]. SHN virgin mice models have shown the effect of lycopene in regulating the differentiation of intra-thymic T cells that could suppress the growth of tumor cells [28]. In *in-vitro* studies on HT-29 cells (human colon cancer cell line), lycopene could suppress the invasion of cancer cells, and expression of MMP-7 (matrix metalloproteinase-7) by inhibiting the phosphorylation of GSK-3β (glycogen synthase kinase-3β), Akt and, ERK1/2 (Extracellular signal-regulated protein kinases 1 and 2), consequently interfered with PI3K (phosphatidylinositol-3-Kinase)/Akt and MAPK (mitogen-activated protein kinase)/ERK signaling pathways. Furthermore, lycopene decreased the amount of nuclear protein including AP-1 (Activator protein-1) and β-catenin [29]. In PC3 cell (prostate cancer cells) line data have shown that lycopene prevented cell proliferation and induction of apoptosis by reducing the expression of AKT2, and increasing the expression of miR let-7f1 (microRNA Lethal-7) in PC3 cells [30]. Evaluations of the effects of lycopene and beta-carotene on AtT20 cells (Mus musculus pituitary tumor) have shown a negative relation to regulating the aggressive form of AtT20 cells. These components could decrease the expression of ACTH (Adrenocorticotropic hormone) and Skp2 (S-phase kinase-associated protein 2), and increase the expression of p27kip1 (Cyclin-dependent kinase inhibitor) and phosphorylated connexin 43. Gap Junction Communication of cancer cells is responsible for the invasion and makes a metastatic form of cancer, lycopene can block these intercellular gap junction communications and control cancer progression [31,32]. In addition, targeted liposome therapy is a routine method for drug delivery to cancer site and can enhance the anti-cancer function of delivered drugs. Encapsulation of lycopene in liposomes, increases antioxidant functions, solubility, bioavailability and stability of this compound [33,34], and also facilitates Bio-accessibility and adequate concentration of lycopene at delivery site [35,36]. Anti-cancer functions of Nano-liposomes of lycopene and lycopene-loaded liposomes are investigated in different cancer studies and are suggested as effective tools for prostate cancer therapy using lycopene [37,38].

4. Prostate cancer

Prostate cancer is one of the most common cancers and the third leading cause of cancer deaths in men. In the United States, the annual incidence of this disease is about 160,000 and its prevalence is around 3.3 million [39]. Different risk factors are involved in induction or progression of an aggressive or non–aggressive form of prostate cancer. Some factors such as; race (American-African), genetics (positive family history), low intake of lycopene (i.e., tomato sauce), and high α-linoleic acid are significantly associated with the incidence of prostate cancer. In regard with the fatal form of prostate cancer, some factors including smoking, high BMI (body mass index), fattiness, α-linoleic and calcium are responsible for the increase in risk [40]. Today, the mortality rate for patients with prostate cancer is reduced by proper diagnosis and new treatment methods for this disease. Monitoring of serum tumor markers and clinical symptoms is helpful for diagnosis of prostate cancer, markers such as PSA (prostate specific antigen) and STEAP (six-transmembrane epithelial antigen of the prostate) family complex which are screening markers, and BRCA1 (breast cancer gene 1) and BRCA2 (breast cancer gene 2) which are more related to aggressive form of cancer. Furthermore, the high expression of ETEAP family complex which acts as channels (gap junction communications) between prostate cells, play an important role in metastasis of cancer [32,41]. There are two categories for treating prostate cancer: first; common medical therapy including surgery, radiation therapy, cryotherapy, hormone therapy and chemo-therapy, and second; new advanced treatment such as vaccine therapy and immunotherapy (cytokines and antibodies) [42,43]. Up-stream and down-stream regulation and treatment affecting signaling pathways of prostate cancer, is a novel strategy for studying and treating by activating or inhibiting up and down stream signaling molecules to diagnose and control this disease. Given that the common treatment for cancer is always with side effects for patients, using natural compounds with anti-cancer functions should be an essential part of these patients' diet. These compounds (i.e. lycopene…) do not have any toxic or side effects to the patient and can be useful in preventing and controlling the manner of cancers.

5. *In-vitro* study of lycopene in prostate cancer cells

In several different studies, it has been shown that the anti-cancer effects of lycopene on prostate cancer cells are mediated by inhibiting cell proliferation, inducing apoptosis, arresting cell cycle, and reducing DNA damages [44,45]. Some *in-vitro* studies showed that the normal

physiological concentration of lycopene in culture media reduces the proliferation of androgen-dependent or independent CaP (cancer of prostate) cell lines [46–48]. The effect of lycopene has been found to be by inhibiting DNA synthesis that could significantly decrease the proliferation and growth of cancer cells in primary PEC (prostate epithelial cancer). Lycopene is protective in controlling the induction and metastatic phase of the prostate disease [1]. Prostate LNCaP (lymph Node Carcinoma of the Prostate) cells in cells culture medium with different concentrations of lycopene demonstrated that the growth and proliferation of cancer cells were decreased, also DNA synthesis, and expression and function of androgen receptors on LNCaP cells are inhibited upon dose-dependent manners [49]. In another *in-vitro* study, the effects of lycopene on different prostate cancer cell lines were demonstrated, which could induce apoptosis and suppress the cell growth in LNCaP (androgen-sensitive), PC3 and VeCaP (androgen–independent) cell lines [50]. Highly moderated expressions of STEAP Ag (as gap junction molecule) are excited on LNCaP and PC3 cell lines [32], and lycopene is able to block the gap junction communications between the cells, and prevent the growth and metastasis of these cancer cell lines [31]. Anti-inflammatory properties of lycopene depends on time, and it has been found to be through the decrease of inflammatory cytokines (i.e. IL1, IL6, IL8 and tumor necrosis factor-α (TNF-α)), and strong apoptotic effects are shown by Annexin V/propidium iodide double-staining assays [16]. Studies on primary PCa cells (human prostate cancer cells) in treating with 5 mg/ml of cis-lycopene during 96 h culture time, showed that the viability of cancer cells was inhibited, and by over-expression of TP53 and Bax (BCL2-Associated X Protein), and down-regulation of Bcl2 (B-cell lymphoma 2), the apoptosis rate was increased [51]. BCO2 (β-carotene-9′,10′-oxygenase 2) enzyme involved in cleavage and metabolism of lycopene which is mainly related to the proliferation and progression of cancer cells, the expression of this enzyme is decreased on prostate cancer tissues and prostate cancer cells. Results showed that treatment with lycopene increased the expression of BCO2 enzyme in an androgen-sensitive cell line that prevented cancer cell proliferation and reduced the NF-κB activity [52]. Anti-cancer and anti-proliferation effects in different concentrations of lycopene in 24 and 48 h incubation with PC3 cell lines, demonstrated that lycopene increased the expression of miR let-7f1, and decreased the expression of AKT2, that led to inhibition of cell proliferation and induction of apoptosis [30]. Lycopene with 1.15 μmol/l concentration in culture of PC3, DU145 and PNT2 (immortalized normal prostate cell line) cell lines, decreased the motility, cell adhesion, and migration manner of prostate cancer cells [53]. Another study has proved that both 20 and 50 μM doses of lycopene had an effect on PC3 and DU145 cell lines in inducing apoptosis with DNA damages, and preventing cell growth and colony formation [54]. Also, lycopene has an effect on cell viability, cell cycles, and apoptosis. These properties have shown that in primary and metastatic prostate cancer cell lines, after 48 and 96 h of treatment, lycopene could reduce the number of cells in G0/G1 phase, enhance G0/G1 phase cycle arrest, enhance the number of cells in S and G2/M phases, and induce the apoptosis by changing Bax and Bcl2 gene expressions [55,56]. And anti-proliferative effect of lycopene on PC3 and DU145 cell lines was proved by10 μM lycopene that positively increased both protein and mRNA expression of PPARγ (peroxisome Proliferator Activated Receptor)-LXRα (liver X receptor α)-ABCA1 (ATP-binding cassette transporter 1) molecules (peroxisome proliferator-activated receptor gamma, liver X receptor alpha, ATP-binding cassette transporter 1) [57]. The unwanted side effects of lycopene on PC-3MM2 (metastatic prostate cancer cell line) was along with the increase in cancer invasion due to the over-expression of urokinase plasminogen activator, and more cell proliferation due to the promotion in expression of connexin 43 expression [58,59]. In Fig. 2, both oxidative and non-oxidative mechanisms are briefly shown as the main pathways that lycopene exerts on cells and reduces the risk of chronic diseases such as cancers and even cardiovascular diseases.

6. *In-vivo* study of lycopene in prostate cancer

Different studies have evaluated the important role of lycopene in increasing or decreasing the markers on patients' serums, and overall controlling cancer progression [44,60,61]. A double-blind placebo-controlled study showed that after 28 days of using lycopene juices, the concentration of lycopene in serum was 80.2 % increased relative to placebo. This could increase antioxidant markers in subjects and lead to the reduction of DNA damages, oxidative stress, and risk of disease [62]. The results of a study men on newly diagnosed with prostate cancer who received lycopene twice a day for 3 weeks, showed that lycopene decreases the risk and growth of prostate cancer cells, and also a decrease in the level of PSA, connexin 43 and IGF-1 was observed in patients [63]. The cancer-protective effects of lycopene (40 mg for 4 weeks) through the decrease in DNA damages and oxidative DNA damages were shown in another human study [64]. In pilot phase II of clinical studies showed that using lycopene supplements in patients could control the speed of PSA markers on Cap [1]. Another randomized, unblended, Phase I clinical trial study similarly showed that the effects of lycopene was to decrease the concentration of PSA serum in high-risk Afro-Caribbean patients with neoplasia, in this study using 30 mg/day of lycopene for 4 months, could raise the serum level of lycopene and reduce the PSA serum level [65]. Using tomato sauce containing lycopene (30 mg/day for 3 weeks) in localized prostate adenocarcinoma patients, have shown an increase in lycopene level of prostate tissues and serum, a decrease in PSA serum level and the DNA damages in both prostate and leukocyte cells in prostatectomy [66,67]. Evaluation of six different doses of lycopene (15, 30, 45, 60, 90, and 120 mg/day) for 1 year, showed the same outcome in patients with relapsed prostate cancer in phase I and II of clinical, trial is along with a reduction in PSA serum and increased concentration of lycopene in serum lycopene [68]. Inverse association between using lycopene and the severity of prostate cancer was evaluated in a clinical trial study that showed the size of tumor and PSA level was decreased in the intervention group [69]. In addition, findings of a pilot study on 40 patients with BPH (benign prostate hyperplasia) received lycopene (15 mg/day for 6 months) has shown the change in PSA level (decrease), lycopene level (increase), progression of cancer (slow) and the size of prostate (small) [70]. Results of the double-blind placebo-controlled clinical trial study, revealed that intervention of lycopene during 3 months have led to the regulation of arachidonic acid, estrogen and androgen metabolism and also have mediated the response of the Nrf2 related to the oxidative stress molecules [71]. Another double-blind, randomized, a placebo-controlled trial study on over than 100 (African-American) men treated with 30 mg/d of lycopene during 21-day before biopsy, showed that the concentration of lycopene was increased and reached to 1.43 μmol/L in plasma and 0.59 pmol/mg in prostate tissues [72]. Receiving 15 mg lycopene (twice a day) in Phase II of clinical trial on patients showed that lycopene could delay the progress of both hormone-sensitive and hormone-refractory prostate cancers [50]. In another human study, daily receiving of 10 mg lycopene for 3 months in 20 metastatic HRPC (hormone-refractory prostate cancer) patients, showed that in the almost all of treated-men progression of disease inversely changed to lower grade and, also the bone pain in patients was reduced [73]. In addition, the anti-angiogenesis function of lycopene in preventing the progression of prostate cancer was proved in a prospective study [74]. One case-control study clarified that the 10 μg/dL concentration of lycopene, could increase the risk of cancer diagnosis (8%) in both benign and metastatic form without biopsy [75]. Without any controversy, a study on 32 HGPIN (high-grade prostatic intraepithelial neoplasia) patients showed that after six-month lycopene therapy (20 − 25 mg/day), no significant effect was observed in regard with the benefits of lycopene related to the progression of cancer or PSA level in these patients [76]. In addition, another cohort study on 75 patients received lycopene for 2 years, did not support the protective role [77]. Also in progressive resistant hormones in patients with

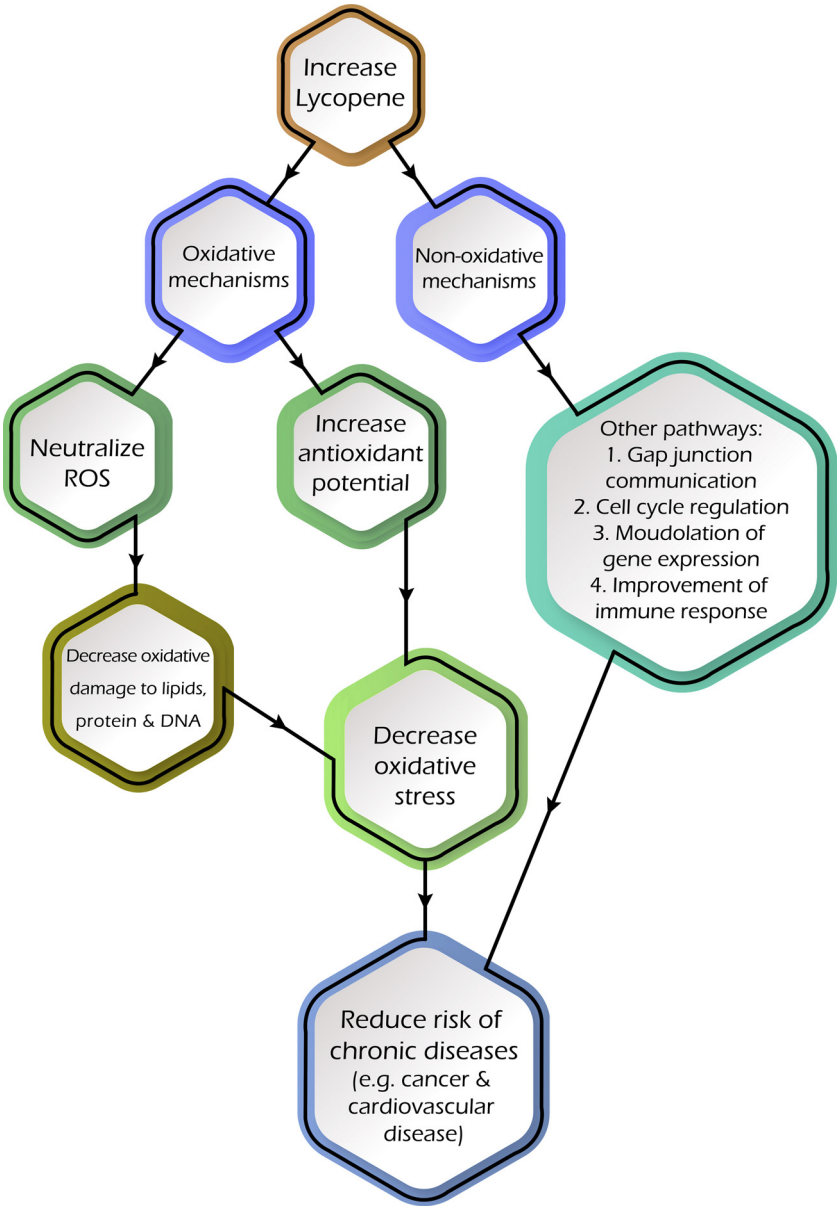

Fig. 2. General mechanisms of action of lycopene.

prostate cancer, 50 % reduction in PSA marker was observed, but the trial showed that 6-month lycopene therapy (15 mg/d) had no clinical benefit for the advanced stage of cancer [78,79]. In addition, in mice models study it was shown that lycopene could not reduce the carcinogenesis in TRAMP (TRansgenic Adenocarcinoma Mouse Prostate) mice [80].

7. The effect of lycopene on signaling pathway of prostate cancer

The signaling pathway is one of the determinative points for normal cell and tissue function, and any changes in the expression of these signaling molecules or transcription factors may cause high or low cell proliferation and lead to a disease. In cancers such as prostate cancer, up and down-regulation of signaling molecules and transcription factors are involved in the outcome of the disease. Therefore, new attempts are on to find new ways or treatments that could modulate this pathway such that cancer is controlled or treated. Studies proved that the best effect of lycopene was related to the red tomatoes. The results showed that the cells culture medium of LN (lymph node), prostate cancer cells could change the expression of some genes with lycopene received (purified, red tomato) patient's sera. Up-regulation of Bax: Bcl-2 ratio, IGFBP-3 (insulin-like growth factor binding protein 3), uPAR (urokinase-Type plasminogen activator receptor), and c-fos (proto-oncogene and homolog of the retroviral oncogene v-fos); and down-regulation of p53, Cyclin-D1, and Nrf-2 have occurred after the incubation of prostate cancer cells with the lycopene received patient's sera in comparison with placebo [81]. Cell culture medium of cis-lycopene with PCa cells showed that over-expression of TP53 and Bax, and down-expression of Bcl2 anti-apoptotic molecule, have led to the promotion of the apoptosis rate in cancer cells [51,55]. NF-κB level and NF-κB activity were decreased on prostate cancer cells after intervention with lycopene [52]. Also, treatment with lycopene in PC3 cancer cell lines was associated with down-regulation of AKT2 [30]. Another anti-proliferative effect of lycopene was done by increasing PPARγ-LXRα-ABCA1signaling molecules in protein and mRNA level [57]. Consumption of lycopene in patients with the risk of colorectal cancer could increase the concentration of circulating IGFBP-1, 2 (insulin-like growth factor of binding proteins-1 and -2) but could not increase insulin-like growth factor (IGF) in patients with the risk of breast [82] and colon cancers [83]. In prostate cancer cell lines anti-proliferatory effect of lycopene

Table 1
Anti-cancer effect of lycopene in different in-vivo and in-vitro experiment.

Type of study (*in-vitro/in-vivo*)	Kind of lycopene	Effect on prostate cancer cells or prostate cancer patients	Ref
Double-blind placebo controlled matched study(*in-vivo* study)	Lycopene juices	Increase concentration of lycopene and antioxidant marker in serum Reduction of DNA damage and oxidative stress Reduction risk of disease	[62]
In-vivo study	Lycopene supplementation	Decrease risk and growth of prostate cancer Decrease of PSA, connexin 43 and IGF-1 levels	[63]
Human study(*in-vivo* study)	Lycopene (40 mg)	Decrease of DNA damage and oxidative DNA damage	[64]
In-vitro studies	Lycopene	Reduce the proliferation of androgen-dependent or -independent Cap cell line	[46,47]
In-vitro study, *In-vivo* study	Lycopene, Lycopene supplementation	Inhibition of DNA synthesis Decrease proliferation and the growth of cancer cells Control the speed of PSA marker on Cap	[1]
Randomized, unblended, Phase I clinical trial study(*in-vivo* study)	Lycopene30 mg/day + multivitamin	Decrease the concentration of serum PSA Increase the serum level of lycopene	[65]
Randomized placebo-controlled study(*in-vivo* study)	Lycopene30 mg/day (tomato sauce)	Increase prostate tissue and serum lycopene level, Decrease of serum PSA level Reduction the DNA damage in both prostate and leukocyte cell	[66]
Phase I-II trial relapsed prostate cancer patients	Lycopene (15, 30, 45, 60, 90, and 120 mg/day for 1 year)	Reduction of serum PSA and increase of serum lycopene concentration	[68]
LnCaP cell line (*in-vitro* study)	lycopene (0.5, 5, 10 and 15 μmol/L)	Decrease the growth and proliferation of cancer cells Decrease of DNA synthesis and the expression and function of androgen receptor	[49]
Clinical trial study(*in-vivo* study)	Lycopene (30 mg)	Reduction in size of tumor and PSA level	[69]
Double-blind placebo-controlled randomized clinical trial study(*in-vivo* study)	Lycopene	Regulation of arachidonic acid, estrogen and androgen metabolism Mediate the response of Nrf2-related oxidative stress molecule	[71]
High-grade prostatic intraepithelial neoplasia (HGPIN) patients (*in-vivo* study)	Lycopene (20 − 25 mg)	No significant effect was observed	[76]
Pilot study on 40 patients with BPH(*in-vivo* study)	Lycopene (15 mg/day for 6 mon)	PSA level (decrease), lycopene level (increase), progression of cancer(slow) and the size of prostate (small)	[70]
Progressive resistant hormone prostate cancer patients (*in-vivo* study)	Lycopene (15 mg/day for 6 mon)	50 % decrease of PSA No clinical benefit	[78]
In-vivo in-vitro study	Red tomato, lycopene	Up regulation of Bax: Bcl-2 ratio, IGFBP-3, uPAR and c-fos Down regulation of p53, Cyclin-D1 and Nrf-2	[81]
Double blind, randomized, placebo-controlled trial study	Lycopene (30 mg) for 21 day	Increased the concentration of lycopene to 1.43 μmol/L in plasma and 0.59 pmol/mg in prostate tissue	[72]
In-vitro studies	lycopene	Induce apoptosis and suppress the cell growth in LNCaP, PC3 and VeCaP cell lines	[50]
In-vitro studies	lycopene	Block the gap junction between the cells and prevent from growth and metastasis	[24]
Phase II clinical trial patients (*in-vivo* study)	Lycopene (15 mg, twice/day)	Delay the progress of both hormone-sensitive and Hormone-refractory prostate cancers	[50]
Metastatic HRPC patients(*in-vivo* study)	Lycopene (10 mg/d for 3 mon)	Reduction of cancer progression Decrease bone pain	[73]
In-vitro study	Lycopene	Decrease of inflammatory cytokines (i.e. IL1, IL6, IL8 and TNF-α) Induction of apoptosis	[16]
In-vitro study	5 mg/ml of cis-lycopene (96 h)	Inhibition of cell viability of cancer cell Induction of apoptosis by overexpression of TP53 and Bax and downregulation of Bcl2	[51]
In-vitro study	lycopene	Overexpression of BCO2 enzyme Reduce cancer cell proliferation and NF-κB level and NF-κB activity	[52]
In-vitro study	Lycopene (2448 h)	Increase the expression of miR let 7f 1 decrease the expression of AKT2 on PC3 cells. Inhibition of cell proliferation and induction of apoptosis	[30]
In-vitro study	1.15 μmol/l lycopene	Decrease the motility, cell adhesion and migration manner of prostate cancer cells in PC3, DU145 and PNT2	[53]
In-vitro study	20 and 50-μM dose of lycopene	Induced apoptosis and DNA damage Prevention from cell growth and colony formation	[54]
Prospective study (*in-vivo* study)	Lycopene	Anti-angiogenesis effect	[74]
In-vitro study	Lycopene	Reduce the number of cells in G0/G1 phase Enhance G0/G1 phase cycle arrest Enhance the number of cells in S and G2/M phases Induce the apoptosis trough change in Bax and Bcl2 gene expression	[55]
In-vitro study	Lycopene (10 μM)	Anti-proliferative effect by increase both protein and mRNA expression of PPARγ-LXRα-ABCA1 molecules	[57]

was directly related to level of IGF-IR (insulin-like growth factor-I receptor), and this was done by suppressing the activation of IGF-IR, preventing IFG-1 from activation or IGF-BP3 expression. The anti-tumor property of lycopene is due to the up-regulation of Bax proteins, down-regulation of cyclin D1 and Bcl2, expression of surviving and inhibition of the activity of AKT kinase [56,84,85]. The effects of lycopene in different *in-vivo* and *in-vitro* experiments have been briefly shown in Table 1.

8. Conclusion

As noted in the review, lycopene can exert its anti-cancer effects through various pathways, including activating and inducing apoptosis, prevents metastasis and progression of prostate cancer by blocking the gap junction molecules and inhibiting the colony formation by decreasing the motility, cell adhesion and migration manner, increasing the anti-oxidative and anti-proliferative effects, decreasing PSA serum level, reducing angiogenesis, and decreasing inflammatory cytokines. These findings suggest that Lycopene and its derivatives could potentially be used in prostate cancer therapy. Since the combined therapy of lycopene in the conjugated form, targeted form, and with adjuvant can show a better effect on preventing or treating prostate cancer disease, it is recommended to investigate and compare the effects of different dosage forms of lycopene on prostate cancer and other malignancies. It is also possible to study the effects of lycopene on the treatment of prostate cancer and malignant tumors by examining novel drug delivery systems, such as solid lipid nanoparticles, liposomes, nanomissiles, liquid crystals, etc.

Declaration of Competing Interest

None.

Acknowledgements

We sincerely thank Research Council of Mashhad University of Medical Sciences for funding this study (No. 960774).

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