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Lycopene: Multitargeted Applications in Cancer Therapy

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Abstract

Cancer is an uncontrolled growth and division of cells, leading to significant morbidity and mortality and economic burden to the society. Natural products as anti-cancer molecules have drawn the attention of researchers and have resulted in the development of many successful anticancer drugs, which include camptothecins, epipodophyllotoxins, vinca alkaloids, and taxanes. Another group of compounds with anti-cancer effects include botanicals (phytochemicals) found in the diet. In recent years, a tomato carotenoid lycopene (LYC) has gained attention for its potential health benefits, especially in prevention and treatment of cancer. The studies suggest that the consumption LYC in food or by itself may reduce cancer risk. However, there are insufficient clinical trial data to support the hypothesis. LYC may play a preventive role in a variety of cancers, especially in prostate cancer. It acts by multiple mechanisms including the regulation of growth factor signalling, cell cycle arrest and/or apoptosis induction, metastasis and angiogenesis, as well as by modulating the anti-inflammatory and phase II detoxification enzymes activities. The effects can be attributed to the unique chemical structure of the carotenoid which confers it a strong antioxidant property. In this chapter, we discuss the chemopreventive and anti-cancer properties of LYC, a dietary carotenoid."

Keywords: phytochemicals, lycopene, cancer, molecular, signaling pathway

1. Introduction

Natural products, which can be defined as simple or complex molecules (primary and secondary metabolites) produced naturally by any organism, constitute a diverse group of substances some of which are part of our food, and others have medicinal properties. Over the

past few decades, there has been a tremendous increase in research on isolation and purification of compounds of botanical origin and establishing the efficacy of these compounds as potential therapeutic and preventive agents. The natural products have received considerable attention as potential drugs, and a large number of medicinal plants and their formulations have been investigated and found useful in cancer chemotherapy [1]. According to an estimate, more than half of potent anticancer drugs have natural product origin [2]. Some of the plant species that have been used for medicinal purpose and suggested for their beneficial effect in cancer are listed in **Table 1**.

Plant species	Preparation	Effect
<i>Acacia nilotica</i>	Aqueous extracts of bark, gum, flower, and leaves	Effective in chemically-induced hepatocellular carcinoma (HCC) [3] and skin papillomagenesis [4]
<i>Aegle marmelos</i>	Hydro-alcoholic extract of leaf	Remission in Ehrlich ascites carcinoma (EAC) [5]
<i>Aloe vera</i>	Extract	Skin carcinoma [6]
<i>Alstonia scholaris</i>	Alkaloid fraction from bark	UV-induced carcinogenesis [7], DMBA-induced skin carcinogenesis [8] and UV-induced hematological disorder [9]
<i>Azadirachata indica</i>	Ethyl acetate and methanolic fractions of the leaves	DMBA-induced mammary carcinogenesis [10] and prostate cancer [11]
<i>Biophytum sensitivum</i>	Alcoholic extract	Dalton's lymphoma ascites (DLA) and EAC [12]
<i>Boswellia serrata</i>	Triterpenediol preparation	Caspase-8 activation and apoptosis [13]
<i>Butea monosperma</i>	Flower extract	Liver cancer [14]
<i>Cassia auriculata</i>	leaf extract	Decrease Bcl-2/Bax ratio [15]
<i>Cassia occidentalis</i>	Aqueous extracts	Inhibit growth of HCT-15, SW-620, PC-3, MCF-7, SiHa and OVCAR-5 cancer cells [16]
<i>Cassia tora</i>	Methanolic extract	Enhance caspase-3 activity of HeLa cells [17]
<i>Cedrus deodara</i>	Lignan mixture	Effect on leukemia cells [18]
<i>Cheilanthes farinose</i>	Fern	HCC [19]
<i>Cinnamomum cassia</i>		Cervical cancer cells (SiHa) [20]
<i>Garcinia indica</i>	Methanolic extract	Colon, breast and liver cancer [21]
<i>Inula racemosa</i>	Ethanol extract of roots	Colon, ovary, prostate, lung, CNS and leukemia cells [22]
<i>Lygodium flexuosum</i>	Extract	Induce apoptosis in hepatoma cells [23]
<i>Ocimum viride</i>	Essential oils	Colorectal adenocarcinoma [24]
<i>Oryza sativa</i>	Methanolic extracts	C6 glioma cells [25]
<i>Phyllanthus niruri</i>	Hydro-alcoholic extract	Skin carcinoma [26]
<i>Piper longum</i>	Methanolic extract	Colon cancer [27]

Plant species	Preparation	Effect
<i>Polyalthia longifolia</i>	Ethanollic stem, bark and leave extracts	EAC and DLA [28]
<i>Rhodiola imbricate</i>	Aqueous extract	Increase ROS and arrest cell cycle progression at G2/M phase in K562 cells [29]
<i>Semecarpus anacardium</i>	Nut milk extract	Effect on leukemic cells from the bone marrow [30], induce apoptosis in breast cancer cells through mitochondria mediated apoptosis [31]
<i>Sesbania grandiflora</i>	Sesbania fraction 2, extracted from the flower	Down-regulate NF- κ B, Bcl-2, p-Akt, cyclooxygenase-2, inhibits proliferation and induced apoptosis in DLA and SW-480 cells [32]
<i>Terminalia arjuna</i>	Ethanollic extract	Liver cancer [33]
<i>Tinospora cordifolia</i>	Extract	Antitumor and chemopreventive [34]
<i>Trachyspermum ammi</i>	Seed extract	Skin and forestomach tumor multiplicity [35]
<i>Withania somnifera</i>	Hydro-alcoholic extract	Colon cancer model [36], cell cycle disruption and antiangiogenic, property [37]
<i>Zingiber officinale</i>	Extract	Suppressed cell proliferation [38]

Table 1. List of some medicinal plants suggested for beneficial effects in cancer.

2. Natural compounds as lead molecules for cancer therapy and their mechanisms of action

Natural substances such as paclitaxel [39], alkaloids and other substances [1] have demonstrated encouraging antitumor activity in human cancer cells *in vivo* and *in vitro*. These molecules act by a variety of mechanisms. For example, paclitaxel, a complex diterpene having a taxane ring with a four-membered oxetane ring and an ester side chain at position C-13, enhances the polymerization of tubulin to stable microtubules and also interacts directly with the microtubules [39]. Other mechanisms of action of antitumor agents include the inhibition of S phase-specific topoisomerase-I (camptothecin) and S and G2 phase-specific topoisomerase-II (etoposide), blockade of G2/M and M/G1 check points (paclitaxel), and prevention of microtubule depolymerization (vinblastine). A new class, commonly known as the vascular disrupting agents (VDA) (e.g., combretastatin A4 phosphate), targets tumor blood vessels. Combretastatin A4 phosphate is a VAD isolated from *Combretum caffrum* and has been reported to be antimitotic and antiangiogenic, along with the microtubule-depolymerizing property [40]. Substances like berberine, a protoberberine alkaloid found in the roots, rhizomes, stems and bark of berberis, goldenseal (*Hydrastis canadensis*) and *Coptis chinensis*, have also been reported to inhibit different types of cancer [41–49]. They act by inhibiting angiogenesis and by other mechanisms in different cancer models. Mahanine, a purified lead molecule derived from the leaves of *Murraya koenigii*, which showed antiproliferative activity in leukemic cells, primary cells of leukemic and myeloid patients and inhibited K562

xenograft growth, activates reactive oxygen species (ROS)-mediated mitochondrial apoptotic pathway, death receptor-mediated signaling differentially in MOLT-3 and K562 cells. Piper betle, reported to decrease the mitochondrial membrane potential and induce apoptosis in primary leukemia cells from CML patients in vitro and K562 xenografts in vivo, can also augment the early ROS production [50]. Withaferin A, which induces apoptosis in HL-60 cells through multiple pathways, also enhances early ROS accumulation leading to loss of mitochondrial membrane potential and cytochrome c release, Bax translocation, caspase activation, and PARP cleavage [51]. It enhanced caspase-8 activity, caspase 3-mediated nuclear cleavage of p65/Rel, which was inhibited by N-acetylcysteine, an antioxidant, suggesting the role of early ROS production in withaferin A-mediated apoptotic signaling. The anticancer molecules, such as betulinic acid, a pentacyclic triterpene, have also been reported to directly activate mitochondria-mediated intrinsic pathway and exhibit antitumor activity [50, 52]. Resveratrol, a phytoalexin found in various food products, induces human promyelocytic leukemia cell differentiation, inhibits cyclooxygenase and hydroperoxidase functions and the development of pre-neoplastic lesions in carcinogen-treated mouse mammary glands as well as tumorigenesis in a mouse skin cancer model [53]. Various other substances isolated from plant material and found to be effective in cancer include: 2-deacetoxytaxinine (from the bark of Himalayan yew, *Taxus wallichiana*) [54], curcumin (from *Curcuma longa*) [55], quercetin 3-O-rutinoside (from the fruits of *Barringtonia racemosa*) [56], 13-epi-sclareol (from the roots of *Coleus forskohlii*) [57], corchorusin-D (from *Corchorus acutangulus*) [58], tetranortriterpenoid methyl angolensate (from the root callus extract *Soymida febrifuga*) [59], oleanonic acid (from *Lantana camara*) [60], longitriol and longimide (from the leaves of *Polyalthia longifolia*) [61], 1-hydroxytectoquinone (from *Rubia cordifolia*) [62], 3-(8'(Z),11'(Z)-pentadecadienyl catechol (from *Semecarpus anacardium* nut) [63], β -sitosterol (from *Asclepias curassavica*) [64], sulfonquinovosyl diacylglyceride (isolated from leaves of *Azadirachta indica*) and nimbolide (from the leaves and flowers of *A. indica*) [65], diallyl disulfide (from *Allium sativum*) [66], arjunic acid (from *Terminalia arjuna*) [67], L-asparaginase, withaferin A, and ashwagandhanolide from (from *Withania somnifera*) [68–70]. Organosulfur from *Allium sativum* (diallyl disulfide and S-allylcysteine) also exhibits good antiproliferative activity [71]. S-allylcysteine is reported to inhibit N-methyl-N'-nitro-N-nitrosoguanidine-induced gastric cancer in rats when administered with tomato carotenoid LYC in a combinatorial approach [72]. A glycoprotein isolated from the bulbs of *Urginea indica* has also been reported to show antitumor activity against an ascites tumor and mouse mammary carcinoma. It inhibited NF-kB, VEGF-induced DNA fragmentation and caspase-3 activation [73].

3. Lycopene

Diets high in fruits and vegetables may reduce the risk of cancers [74–78]. Tomato and tomato-based products have been found to be effective in the stomach, lung and pleural, colorectal, oral/laryngeal/pharyngeal, esophageal, pancreatic, prostate, bladder, breast, cervical and ovarian cancers [79]. Lycopene (LYC) ($C_{40}H_{56}$; Molar mass, 536.873 g/mol) is a bright red-colored carotenoid pigment found in red fruits and vegetables particularly

tomato, carrot, watermelon, guava, etc., (but not in all red fruits, like strawberries, or cherries) and also in some vegetables that are not red, such as parsley and asparagus. The beneficial effects of tomato on health have been attributed to the presence of LYC. LYC is a highly unsaturated, straight-chain hydrocarbon containing 11 conjugated and two non-conjugated double bonds (**Figure 1**).

It is a non-provitamin A carotenoid. The biological significance of carotenoids has been well established and documented. The β -carotene, for example, is converted into retinal, retinoic acid, and apocarotenoids, which plays a very important role in human/animal

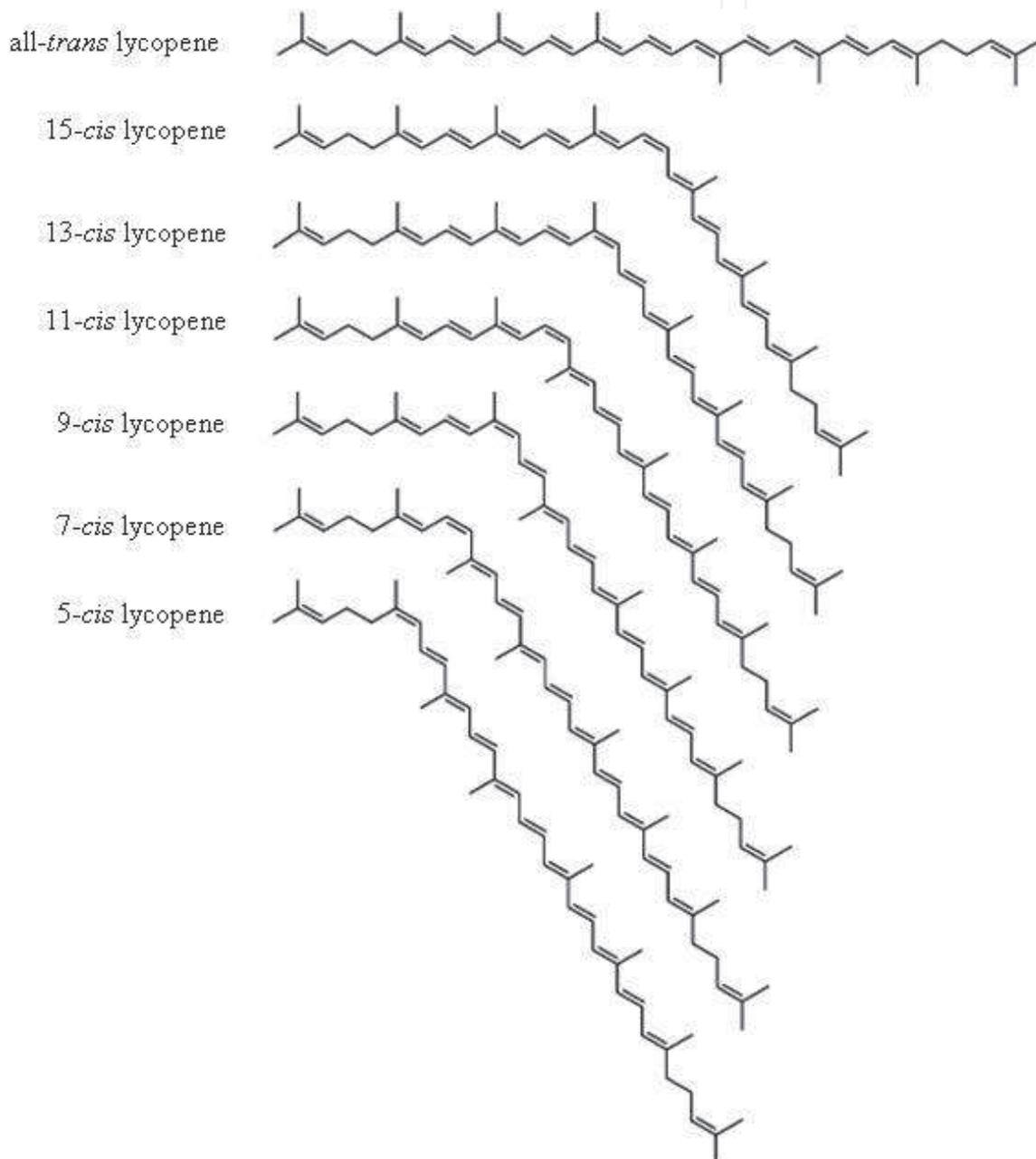


Figure 1. Chemical structures of lycopene isomers.

physiology [80]. LYC is non-provitamin A carotenoid which is not converted to vitamin A. It is a major component found in the serum and other tissues and has been inversely related to cancer and cardiovascular diseases [81]. The molecule acts as an antioxidant and has been reported to have beneficial effects, which can be attributed to its unique chemical structure [82]. LYC can modulate the intercellular gap junction communication, hormonal and immune system, and metabolic pathways.

LYC exists predominantly in trans-configuration, the most thermodynamically stable form, and as a polyene, it undergoes cis-trans isomerization induced by light, thermal energy or chemical reactions. In human plasma, LYC is an isomeric mixture containing 50% of total LYC as cis isomers. All-trans, 5-cis, 9-cis, 13-cis, and 15-cis are most commonly identified isomeric forms of LYC. LYC is poorly absorbed when ingested in its natural trans-form found in tomatoes. Heat processing of tomatoes and tomato products increases the bioavailability of LYC by inducing isomerization of LYC to the cis form [83]. LYC, which when oxidized with potassium permanganate and by atmospheric oxygen catalyzed by a metalloporphyrin, is converted into apo-lycopenals and apo-lycopenones [84]. In addition, a number of other apo-lycopenals have been suggested in fruits, vegetables, and human plasma [85–87].

4. Lycopene: its role and mechanisms of action in cancer

Carotenoid-rich foods have been associated with reduced risk of cancer, such as the prostate and other cancers by various mechanisms [81, 88–95]. The enhanced cytotoxic and apoptosis inducing the activity of LYC has been recorded in different cancer cell lines [96]. The influence of LYC and its oxidation products on the levels of intracellular ROS in three different cell lines has been studied, and in all the cases, the oxidation products increased the ROS levels than the LYC- and control-treated cells. In MCF-7 cells, ROS in control- and LYC-treated groups was lower by 16.3 and 15.5% than in oxidation product treated cells [96].

A number of mechanisms of action have been proposed to explain the anticarcinogenic action of LYC. These include: (i) the inhibition of cancer cell proliferation and induction of differentiation (of cancer cells) by modulating the expression of cell cycle regulatory proteins, (ii) modulation of the IGF-1/IGFBP-3 system, (iii) inhibition of oxidative DNA damage, (iv) modulation of redox signaling, (v) upregulation of gap-junctional gene connexin 43 (Cx43) and increased gap junctional intercellular communication, (vi) inhibition of 5-lipoxygenase, (vii) modulation of carcinogenic metabolizing enzymes, (viii) modulation of immune function, (ix) modulation of IL-6 and androgen, (x) inhibition of IL-6 and androgen, (xi) inhibition of 5-lipoxygenase, (xii) modulation of carcinogen metabolizing enzymes and (xiii) modulation of immune function [97], (xiv) reduction of oxidative stress by modulating ROS-producing enzymes (CYP-P450 enzymes, NADPH oxidase, iNOS, COX-2 and 5-LOX), (xv) inducing antioxidant/detoxifying phase II enzymes (also chemical interaction with radioactive materials), NQO1 and GST [98], (xvi) regulation of nuclear factor E2-related factor 2-antioxidant response element (Nrf2-ARE) system [99], and (xvii) inactivation of growth factor (PDGF, VEGF and IGF)-induced PI3K/AKT/PKB and Ras/RAF/MAPK signaling pathways [100] (**Figure 2**)

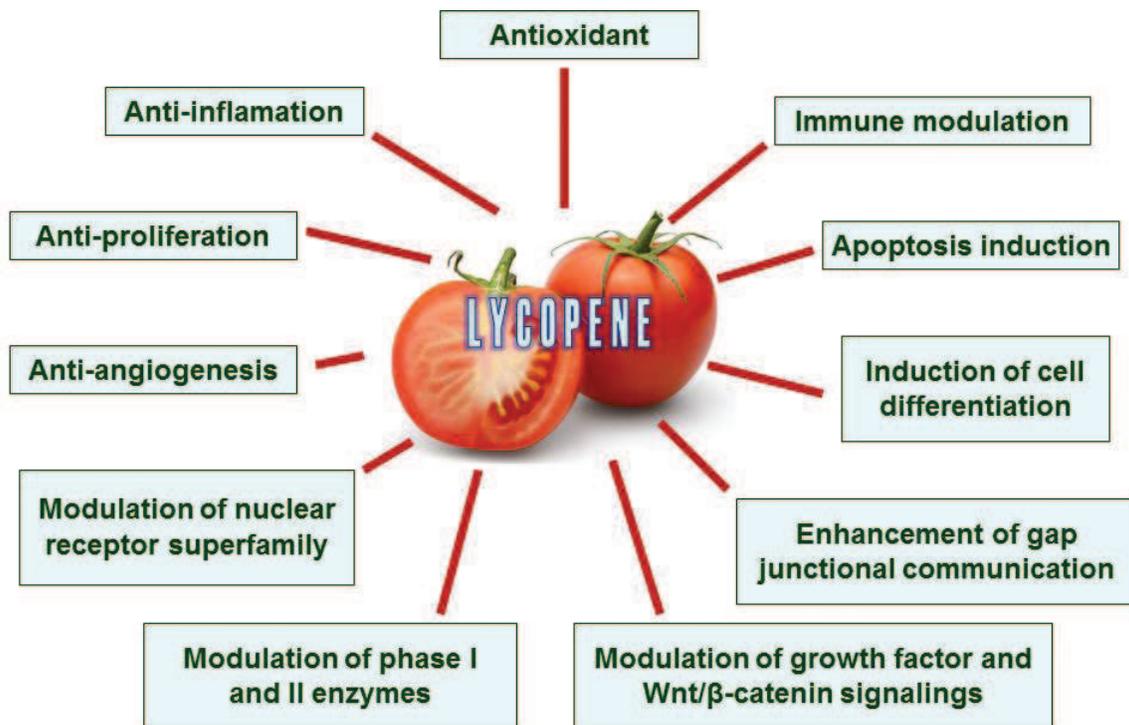


Figure 2. Mechanisms of cancer chemoprevention by lycopene.

4.1. Prostate cancer

The beneficial effects of LYC in prostate cancer (PC) have been extensively reported. A significant inverse correlation between PC and plasma LYC concentration [odds ratio (OR) = 0.17, P-trend = 0.005] has been found between the highest and lowest quintiles of intake [101]. In several experimental studies, LYC has been suggested to suppress PC in vitro and in vivo [102, 103]. It was found to down-regulate the expression of protein kinase B (AKT2) and up-regulate miR-let-7f-1 expression in PC3 cells. Reintroduction of miR-let-7f-1 into PC3 cells was able to inhibit cell proliferation and induce apoptosis. Further research has shown that up-regulation of miR-let-7f-1-targeted AKT2 and AKT2 in PC3 cells can alleviate the effects induced by miR-let-7f-1 [104]. In a recent study published by Tan et al. [105], mice fed semi-purified diets containing 10% tomato powder or 0.25% LYC beadlets up to 18 weeks had higher serum concentrations of total, 5-cis, other cis and all-trans as compared with control in β -carotene 9',10'-oxygenase (BCO2) +/+ mice. The incidence of PC was lower in animals fed with tomato and LYC when compared with control group. The ability of LYC and tomato to inhibit prostate carcinogenesis was significantly attenuated by loss of BCO2 (P-interaction = 0.0004 and 0.0383, respectively), although the BCO2 genotype did not significantly alter the PC outcome in mice fed with the control AIN-93G diet alone. In another study, the treatment with LYC or metabolite with apo-10-lycopenal increased the BCO2 expression and decreased cell proliferation in androgen-sensitive cell lines, but did not alter BCO2 expression or cell growth in LYC androgen-resistant cells. In particular, restoration of BCO2 expression in PC cells prevented cell proliferation and colony formation independent of LYC exposure [106]. Yang et al. [107] reported that a low or

high dose of LYC (4 and 16 mg/kg) and a single β -carotene (16 mg/kg) twice weekly for 7 weeks strongly inhibited the tumor growth, as evidenced by the decrease in tumor volume and tumor weight in thimeric nude mice implanted subcutaneously with human androgen-independent prostate carcinoma PC-3 cells. At high dose level, LYC and β -carotene significantly reduced the expression of PCNA (proliferating cellular nuclear antigen) in tumor tissues and increased insulin-like growth factor-binding protein-3 levels in the plasma. In addition, LYC supplementation at high dose level significantly reduced vascular endothelial growth factor (VEGF) in the plasma. Tang et al. [94] also showed that supplemental LYC inhibited the growth of DU145, a human prostate tumor cell line, transplanted into BALB/c nude mice.

Several studies supporting the relationship between consumption of tomato products and a reduced incidence of PC have come from the Health Professionals Follow-Up Study. In a randomized two-arm clinical trial, patients who have diagnosed PC and scheduled to undergo radical prostatectomy were randomly assigned to either 30 mg of oral LYC supplementation or no intervention for 3 weeks prior to surgery. The study reported that the plasma prostate-specific antigen (PSA) level decreased by 18% in the intervention group, while it increased by 14% in the control group over the study period. In the intervention group, 11 of 15 patients (73%) had no involvement of surgical margins and/or extraprostatic tissues with cancer, compared to 2 of 11 patients (18%) in the control group. Twelve of 15 patients (80%) in the LYC group had tumors that measured 4 cc or less, compared to 5 of 11 (45%) in the control group [108]. In the same study, Kucuk et al. noted that the expression of Cx43 in the malignant part of the prostate glands was higher in LYC group than the control group. Prostatic tissue LYC levels were 47% higher in the intervention group compared to control group [108]. Phase II randomized clinical trial of 15 mg of LYC supplementation twice a day for 3 days before radical prostatectomy showed a decrease in plasma IGF-I levels, but no significant change in Bax and Bcl-2 [109]. Recently, Paur et al. [110] showed that post hoc, exploratory analyses within intermediate risk patients based on tumor classification and grade and Gleason post-surgery revealed that median PSA decreased in the tomato group as compared to controls (-2.9 and +6.5%). Separate post hoc analyses showed that the median PSA values reduced by 1% in patients with the highest increase in plasma LYC, selenium and C20:5 n-3 fatty acid, compared with the 8.5% increase in patients with the lowest increase in LYC, selenium, and C20:5 n-3 fatty acid. In addition, PSA decreased in patients with the highest increase in LYC ($p = 0.009$). In addition, it was showed that neither pre-diagnosis nor post-diagnosis dietary LYC intake was associated with PC-specific mortality (PCSM) (fourth and first quartile HR = 1.00, 95% GA 0.78–1.28, HR = 1.22, 95% GA 0.91–1.64, respectively). Also, neither pre-diagnosis nor post-diagnosis consumption of tomato products was associated with PCSM. Among subjects with high-risk cancers (T3-T4 or Gleason score 8–10 or nodal involvement) consistently reporting LYC intake \geq median on both postdiagnosis surveys was associated with lower PCSM (HR = 0.41, 95% GA 0.17–0.99, based on ten PCSM cases consistently \geq median intake compared to consistently reporting intake <median [111]).

4.2. Breast cancer

In vitro and in vivo studies suggest that intake of LYC-containing foods may reduce breast cancer risk. Assar et al. [112] have recently reported that LYC inhibits prostate as well as breast

cancer cell growth at physiologically relevant concentrations $\geq 1.25 \mu\text{M}$. Similar concentrations also caused a 30–40% reduction in I κ B phosphorylation (which regulates the activity of NF- κ B [113] as determined by Western blot analysis. However, immunofluorescence staining of LYC-treated cells showed a significant suppression of NF- κ B p65 subunit nuclear translocation ($\geq 25\%$) caused by TNF. In another in vitro study reported by Gloria et al. [114], a significant decrease in the number of viable breast cancer cells treated with LYC and beta-carotene carotenoids were observed. Carotenoids promoted cell cycle arrest and then decreased cell viability in the majority of cell lines after 96 h from the controls. In addition, when cells were treated with carotenoids, an increase in apoptosis was observed in cell lines. Cui et al. [115] reported that LYC intake was inversely associated with estrogen and progesterone receptor positive breast cancer risk in postmenopausal women ($n = 84,805$), averaging 7.6 years (RR = 0.85 for high quartile of intake as compared with the lowest quartile of intake, P -trend = 0.064). In an animal study, the incidence of breast cancer was found to be inhibited by LYC (70%), genistein (60%) and their combination (40%). Tumor weight was reduced by 48, 61 and 67% with LYC, genistein and LYC + genistein, respectively, and the mean tumor volume decreased by 18, 35, and 65%, respectively. Administration of the combination of LYC and genistein suppressed breast cancer development and was associated with a decrease in malondialdehyde (MDA), 8-isoprostane and 8-OHDG levels, and increase in serum LYC and genistein. Animals treated with DMBA developed breast cancer associated with increased expression of Bcl-2 in breast tissues and decreased expression of Bax, caspase-3, and caspase-9. The combination of genistein and LYC was more effective than either agent alone to inhibit DMBA-induced breast tumors and to modulate the expression of apoptosis-associated proteins [116]. Recently, in a randomized, placebo-controlled, double-blind, cross-over study, Voskuil et al. [117] found that tomato extract supplementation (30 mg/day LYC) for 2 months reduced free insulin-like growth factor-I (IGF-I) in premenopausal women with a high risk of breast cancer ($n = 36$) I) by 7.0%. Al-Malki et al. [118] demonstrated that combined treatment of LYC and tocopherol (LYC-Toco) caused a reduction in MDA and nitric oxide (NO) in serum and breast tissues in LYC-Toco group than the LYC alone group. Superoxide dismutase, catalase, and glutathione peroxidase activities were significantly higher when compared to rats treated with LYC alone. Serum alanine transaminase, aspartate aminotransferase, total bilirubin and malondialdehyde, which increased in the group of rats treated with diethylnitrosamine (DEN), and hepatic antioxidant enzymes (catalase, superoxide dismutase, and glutathione peroxidase) and glutathione, which decreased in the cancerous group, improved in LYC-treated animals [119]. LYC also caused a reversal and reduced NF- κ B and cyclooxygenase-2, consequently increasing Nrf2/HO-1 expression and inhibition of inflammatory cascade, thereby activating the antioxidant signaling. LYC also reduced increases in phosphorylated mammalian targets for phosphorylated rapamycin (p-mTOR), phosphorylated p70 ribosomal protein S6 kinase 1, phosphorylated 4E-binding protein 1, and protein kinase B.

4.3. Gastric and colorectal cancer

Studies have also reported a positive correlation between LYC or tomato product consumption and gastric and colorectal cancers [120, 121]. Although there has been a series of epidemiological studies investigating the relationship between LYC or LYC-rich food and

serum/plasma LYC concentration and colorectal cancer risk, the results of these studies have not been consistent [79, 122]. Teodoro et al. [123] have demonstrated a significant reduction in the number of viable cells in human colon adenocarcinoma cells (HT-29), human colon carcinoma cells (T-84), and breast cancer cell line (MCF-7) after 48 h of treatment with LYC. LYC stimulated cell cycle arrest followed by reduced cell viability in the majority of cell lines after 96 h as compared to controls. In addition, when cells were treated with LYC, an increase in apoptosis was observed in four cell lines (T-84, HT-29, MCF-7, and DU145). LYC has also been reported to inhibit cell proliferation in human colon cancer HT-29 cells with IC₅₀ value of 10 μ M. LYC treatment also suppressed Akt activation and non-phosphorylated β -catenin protein levels in human colon cancer cells. In addition, LYC significantly increased the nuclear cyclin-dependent kinase inhibitor p27(kip) abundance and inhibited the phosphorylation of retinoblastoma tumor suppressor protein in human colon cancer cells [124]. In another study, it was shown that inhibition of cell growth by tomato digestate was dose dependent and resulted from cell cycle arrest at G₀/G₁ and G₂/M phase and progression by apoptosis induction. Down-regulation of Cyclin D1, Bcl-2, and Bcl-x1 expression has also been observed [125]. In a study conducted by our research group [126], we showed that 5% of the tomato powder added to the diet reduced the aberrant crypt foci (ACF) ratio and also reduced adenocarcinoma development and azoxymethane (AOM)-induced colorectal cancer formation in rats. In addition, the addition of tomato powder indicated that it exhibits chemopreventive activity by regulating Nrf2/HO-1 signaling pathway in colorectal tissue while inhibiting cyclooxygenase-2 (COX-2) expression and inducing apoptosis via the NF- κ B pathway. Dias et al. [127] reported that treatment with LYC, synbiotics or a combination thereof significantly increased apoptosis, decreased PCNA and p53 labeling indices, and classical ACF and mucin-negative ACF development. In addition, a lower genotoxicity of fecal water was also detected in groups treated with the chemopreventive agents. The additive/synergistic effect of combined treatment with LYC/synbiotics was observed only for the fecal water genotoxicity and mucin-negative ACF parameters. In a study in a mouse xenograft model, Tang et al. [128] reported that LYC suppressed the nuclear expression of PCNA and β -catenin proteins in tumor tissues. LYC consumption may also increase the nuclear levels of the E-cadherin adherent molecule and the cell cycle inhibitor p21 (CIP1/WAF1) protein. The inhibitory effects of LYC were associated with the suppression of COX-2, PGE (2) and phosphorylated ERK1/2 proteins. In addition, the inhibitory effects of LYC were inversely correlated with plasma levels of matrix metalloproteinase 9 (MMP-9) in tumor-bearing mice.

In a randomized, placebo-controlled, double-blind crossover study, the tomato-based LYC supplementation (Lyc-o-Mato[®], 30 mg/day LYC) for 8 weeks has been reported to increase serum insulin-like growth factor binding protein-1 (IGFBP-1) concentration in men and women with high risk for colorectal cancer [129]. The group also reported that the serum IGFBP-2 concentration in men and women increased by 8.2 and 7.8%, respectively. In a double-blind, randomized, placebo-controlled trial, Walfisch et al. [130], a reduction of 25% in plasma IGF-I concentration was reported in 30 patients waiting for colectomy surgery, supplemented with Lyc-o-Mato[®]. In the same study, a 24% reduction in IGF-I/IGFBP-3 ratio was also observed. In another study, 20 healthy individuals participated in a double-blind crossover dietary intervention and consumed a tomato juice drink (250 ml Lyc-o-Mato[®] beverage, 5.7 mg LYC, 3.7 mg

phytoene, 2.7 mg phytoplankton, 1.8 mg α -tocopherol) and a 26-day wash between each placebo drink [131] for 26 days each. The blood plasma levels of IGF-I were found to be inversely correlated with the consumption of LYC. In yet another study, 20 healthy subjects participated in a double-blind crossover dietary intervention and consumed a tomato juice beverage (250 ml of Lyc-o-Mato® drink) and a 26-day wash between each placebo drink, the plasma IGF-I levels were inversely correlated with the intake of LYC [131].

LYC has also been reported to inhibit *Helicobacter pylori*-induced increases in ROS, 8-OH-dG, and apoptosis by increasing Bax and decreasing Bcl-2 expression as well as PARP-1 cleavage, changes in cell cycle distribution, double-stranded DNA breaks, activation of ataxia-telangiectasia-mutated (ATM) and ATM and Rad3-related (ATR)-mediated DNA damage response in gastric epithelial AGS cells [132]. The administration of LYC (50, 100 and 150 mg/kg body weight) in gastric carcinoma-induced rats up-regulated the redox status and immune activities and was useful in reducing the gastric cancer risk [133].

4.4. Liver cancer

The frequent consumption of tomatoes and tomato-based products has been suggested to lower the risk of other cancers, such as the liver, renal and ovarian cancers. LYC can block the growth on human Hep3B hepatoma cells in a dose-dependent manner and at the same time has been shown to inhibit metastasis in SK-Hep 1 human hepatoma cell line [134, 135]. In a study conducted by our research group, we reported a decrease in serum alanine transaminase, aspartate aminotransferase, total bilirubin and malondialdehyde by LYC in the diethylnitrosamine (DEN)-treated animals. LYC increased the hepatic antioxidant enzymes (catalase, superoxide dismutase, and glutathione peroxidase) and glutathione and reduced the NF- κ B/cyclooxygenase-2. The Nrf2/HO-1 expression increased, and the inflammatory cascade inhibited by LYC, suggesting an activation of the antioxidant signaling by LYC. In this study, LYC reduced the increases in phosphorylated mammalian targets of phosphorylated rapamycin (p-mTOR), phosphorylated p70 ribosomal protein S6 kinase 1, phosphorylated 4E binding protein 1, and protein kinase B [119]. In another study on DEN-induced hepatocarcinogenesis in rats, LYC was reported to be effective against preneoplastic foci in the liver by decreasing the size of the liver; whereas LYC administration in another animal study did not reduce the risk of spontaneous liver cancer [136, 137]. The LYC-added tomato paste has been reported to be protective against oxidative stress induced by N-nitrosodiethylamine (NDEA) in rats. It decreases the microsomal lipid peroxidation in the liver and significantly reduced plasma protein carbonyl levels [138]. LYC supplementation also prevents liver-specific carcinogenic DEN-induced of hepatic preneoplastic foci and macroscopic nodules in rat hepatic glutathione S-transferase placental-form positive foci in rats that developed spontaneous liver tumors and ameliorated DEN-initiated, HFD (high-fat diet)-promoted precancerous lesions [139, 140]. It was effective in decreasing NASH-promoted, DEN-initiated hepatocarcinogenesis in rats [136]. Apo-10'-lycopenoic acid, a LYC metabolite produced by β -carotene-9',10'-oxygenase (BCO2) inhibited hepatic inflammation and liver inflammation induced by carcinogen-initiated high-fat diets [98, 141] showed that LYC supplementation (100 mg/kg diet) for 24 weeks decreased hepatic proinflammatory signal (phosphorylation

of NK- κ B p65 and STAT3, IL6 protein) and inflammatory foci in wild-type mice. In contrast, the protective effects of LYC in BCO2-KO were related to reduce hepatic endoplasmic reticulum stress-mediated unfolded protein response, the ER(UPR), through decreasing ER(UPR)-mediated protein kinase RNA-activated like kinase-eukaryotic initiation factor 2 α activation, and inositol-requiring 1 α -X-box-binding protein 1 signaling. LYC treatment in BCO2-KO mice inhibited carcinogenic signals, including Met mRNA, β -catenin protein and mTOR complex 1 activation associated with increased liver microRNA (miR)-199a/b and miR214 levels [141]. The connection between LYC and aflatoxin B1 (AFB1) initiated HCC has also been examined [142], and in recent studies [143], the hepatocarcinogenesis pathway has been linked to the activation of the oxidative stress-inflammatory pathway in rat liver.

4.5. Renal cancer

Previous research has shown that micronutrients consumed through diet or dietary supplementation, including vitamin E and carotenoids, can inhibit oxidative DNA damage, mutagenesis and tumor growth [144, 145]. However, many studies have shown that there is no significant association between RCC and antioxidant micronutrient intake [146], while others suggest supportive evidence that some micronutrients may have a protective effect [147]. Increased uptake of LYC in postmenopausal women in the Women's Health Initiative (WHI) was inversely associated with RCC risk ($p = 0.015$); compared with the lowest quartile of LYC intake, the highest quartile of intake was associated with a 39% lower risk for RCC (hazard ratio, 0.61, 95% confidence interval, 0.39–0.97) when compared with the lowest quartile of LYC intake [145]. It was also reported that no other micronutrient was significantly associated with RCC risk [145]. Another case-control study reported that the intake of vegetables was associated with a reduction in the risk of RCC (OR 0.5; 95% CI 0.3, 0.7; P trend = 0.002) [148]). In the same study, it was reported that both β -cryptoxanthin and LYC were associated with reduced risks, but when both were included in a mutually adjusted backward stepwise regression model, only β -cryptoxanthin remained significant (OR 0.5; 95% CI 0.3, 0.8). When other micronutrients and fiber types were investigated together, only vegetable fiber and β -cryptoxanthin showed significant trends. They also reported that these findings are stronger for people over 65 years of age. Additionally, among nonsmokers, low intake of cruciferous vegetables and fruit fiber was also associated with increased risk of RCC (P interaction = 0.03); similar reverse relationships were found for β -cryptoxanthin, LYC and vitamin C [148]. LYC has also been found to decrease the tumor presence and the average number of renal carcinomas in a small animal model (rat) for studying renal cell carcinoma (RCC) [149]. In the LYC group, the tumor counts decreased and as the LYC supplement increased from 0 to 200, the numbers tended to decrease linearly. Control rats fed only on a basal diet had a greater length of tumors (23.98 mm) than those fed to LYC supplementation groups (12.90 and 2.90 mm) (11.07 mm). In addition, when LYC increased from 0 to 200 mg/kg, tumor length decreased. It tended to decrease linearly. All tumors showed strong staining with antibodies to mTOR, phospho-S6, and EGFR.

4.6. Bladder cancer

LYC supplementation has been reported to exhibit a non-significant trend after administration of N-butyl-N-(4-hydroxybutyl) nitrosamine to reduce the number of bladder transitional

cell carcinomas in rats [150]. In a case-control study involving 569 bladder cancer cases and 3123 controls, the relative risk for bladder cancer was 1.08, which compared the highest and lowest rates of LYC uptake [151]. However, in a cohort study, serum LYC levels in bladder cancer cases were found to be lower than those of compatible controls [152]. In another case-control study with 84 cases and 173 controls, OR for bladder cancer was 0.94 (95% CI 0.89–0.99) in the highest quartile of plasma LYC intake when compared to lowest after controlling for age, sex, education, and pack-years of smoking [153].

4.7. Lung cancer

Many studies have shown that smokers and lung cancer patients tend to be lower plasma concentrations of β -carotene, retinol, LYC, β -cryptoxanthin and α -tocopherol [154]. Graham et al. [155] have treated LYC solutions with human plasma and isolated LDL with cigarette smoke and observed the depletion of all(E)-chylopen, 5 (Z)-chylonopen and β -carotene. Depletion of all(E)-lycopenin ($15.0 \pm 11.0\%$, $n = 10$) was greater than 5 (Z)-lycopenin ($10.4 \pm 9.6\%$) or β -carotene ($12.4 \pm 10.5\%$) in plasma. LDL was found to be more sensitive to both all(E)- and 5 (Z)-lycopenin than β -carotene (20.8 ± 11.8 , 15.4 ± 11.5 and $11.5 \pm 12.5\%$, $n = 3$). It was also reported that smoke exposure reduced the concentrations of LYC in plasma and lung tissue of LYC supplemented ferrets, which was consistent with the National Health and Nutrition Examination survey III finding that smokers had lower serum levels of LYC compared to nonsmokers [156]. In one study, the concentration of LYC in lungs was $1.2 \mu\text{mol/kg}$ lung tissue in ferrets fortified with LYC at a dose of 60 mg/day, and this did not cause a harmful effect, instead it prevented the induction of lung squamous metaplasia and cell proliferation induced by smoke exposure [157]. On the other hand, intake of tomato or tomato products including LYC has been associated with a lower risk of lung cancer [158]. In cell culture, LYC has been shown to inhibit the nitration of proteins and DNA strand breakage caused by peroxynitrite treatment of hamster lung fibroblasts [159]. Apo-100-lycopenoic acid has been reported to inhibit the growth of the normal human bronchial epithelial cells, BEAS-2B immortalized normal bronchial epithelial cells, and A549 non-small cell lung cancer cells [158]. LYC dissolved in drinking water at a dose of 50 ppm significantly reduced diethylnitrosamine (DEH), methylnitrosourea (MNU), and dimethylhydrazine (DMH)-induced lung adenomas along with carcinomas in male mice [160]. The inhibitory effect of apo-100-lycopenoic acid was associated with decreased cyclin E, inhibition of cell cycle progression and an increase in cell cycle regulator p21 and p27 protein levels. In addition, apo-100-lycopenoic acid trans-activated the retinoic acid receptor β (RAR β) promoter and initiated the expression of RAR β . In another animal study, the incidence of lung adenomas and carcinomas in male mice receiving 50 ppm LYC in addition to diethylnitrosamine (DEN), N-methyl-N-(MNU) and 1,2-dimethylhydrazine (DMH) was lower than the incidence seen in non-LYC recipients (18.8 versus 75.0%) [161].

5. Concluding remarks

Some plant and plant-based products and their active ingredients exhibit significant anti-tumor properties. They may act by blocking the cell cycle checkpoints (paclitaxel) and specific enzymes, such as the S-phase specific topoisomerase-I (camptothecins) and S and G2

phase-specific topoisomerase-II (etoposide), and by preventing the microtubule polymerization (vinblastine), as well as by various other mechanisms. Diallyl disulfide, limonoids, azadirachtin, pentacyclic triterpenediol, theaflavins, curcumin, lupeol, and AECHL-1 [162–169], for example, modulate the p53-regulated pathways. Bromelain, theaflavin, thearubigin, curcumin, E-piplartine (trans-piplartine), 3 β -hydroxylup-20(29)-ene-27,28-dioic acid, withanolide D, withaferin A [70, 170–176] affect MAPK-regulated pathways. The other pathways include death receptors (example, theaflavins [177] and ROS-mediated pathways (isointermedeol, mahanine, chlorogenic acid, withaferin A [50, 51, 178]. The β -sitosterol, which has a significant anticancer activity against colon cancer, acts by scavenging ROS and suppressing the expression of PCNA [62]. Sesquiterpene isointermedeol (ISO), which is a major constituent of *Cymbopogon flexuosus* (lemon grass) and inhibitor of proliferation of human leukaemia HL-60 cells, also induces ROS production with the concomitant loss of mitochondrial membrane potential, DNA laddering, and apoptotic body formation.

LYC, which is a highly unsaturated, straight-chain hydrocarbon, is reported to be beneficial in cancers, especially the prostate cancer. It can reduce oxidative stress by modulating ROS-producing enzymes (CYP-P450 enzymes, NADPH oxidase, iNOS, COX-2, and 5-LOX) and inducing antioxidant/detoxifying phase II enzymes [98]. These phase II enzymes are regulated by the nuclear factor E2-related factor 2-antioxidant response element (Nrf2-ARE) system. The Nrf2/HO-1 signaling is suggested to be an important primary target for chemoprevention (cisplatin-induced nephrotoxicity) by LYC. LYC can also decrease inflammation by inhibiting NF- κ B [99]. It can inhibit the proliferation and induction of differentiation of cancer cells by modulating the expression of cell cycle regulatory proteins, modulating the IGF-1/IGFBP-3 system and other mechanisms including the prevention of oxidative DNA damage and modulation of the immune function, as well as the inactivation of growth factor (PDGF, VEGF, and IGF) induced PI3K/AKT/PKB and Ras/RAF/MAPK signaling pathways [100].

6. Future perspective

Overall, the research articles reviewed in this chapter provide convincing evidence suggesting a role for LYC in cancer, particularly in prostate cancer. LYC may act by a variety of mechanisms, some of which could be linked to the antioxidant activity of this non-pro-vitamin-A carotenoid. Lycopene supplementation could be a potential candidate for future clinical trials in prostate cancer and other cancers both as a preventive and therapeutic agent and in combination with other therapies. This phytochemical offers great promise in integrative oncology and warrants further clinical evaluation with careful attention to individualized dose escalation until an effective and safe dose is found.

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