Lycopene as a potential anticancer agent: Current evidence on synergism, drug delivery systems and epidemiology (Review)

SILIANG YIN[1], XIUQING XU[1], YI LI[1], HENG FANG[2] and JUNLING REN[2]

[1]Pharmaceutical Research Institute, Guangshengyuan Traditional Chinese Medicine Co., Ltd., Datong, Shanxi 037000, P.R. China; [2]GAP Center, Heilongjiang University of Chinese Medicine, Harbin, Heilongjiang 150040, P.R. China

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Abstract. Plant-derived natural compounds are an important source of anticancer drugs. Lycopene, commonly referred to as 'plant gold', is a powerful antioxidant with multiple health benefits. It may be associated with a reduction in the morbidity and mortality of several types of cancer, making it a promising anticancer agent. The present review summarizes the synergistic effects of lycopene as a dietary supplement with other chemotherapy drugs or nutrients, for the enhancement of anticancer effects or the reduction of side effects from chemotherapy drugs. Moreover, due to its low water solubility, the development of novel drug delivery systems may improve the bioavailability of lycopene. By summarizing epidemiological research, the present review highlights the current clinical research status and limitations of lycopene, with the aim to provide useful information and guidance for future research on the anticancer effects of lycopene.

Correspondence to: Professor Junling Ren, GAP Center, Heilongjiang University of Chinese Medicine, 24 Heping Road, Harbin, Heilongjiang 150040, P.R. China
E-mail: junlingren@126.com

Abbreviations: 5-FU, 5-fluorouracil; ADT, androgen deprivation therapy; CRC, colorectal cancer; CRPC, castration-resistant prostate cancer; GSH, glutathione; HGPIN, high-grade prostatic intraepithelial neoplasia; HR, hazard ratio; IGF-1R, insulin-like growth factor-1 receptor; IGFBP3, IGF binding protein 3; MDA, malondialdehyde; NI, niosome; NHB, non-Hispanic Black; NHW, non-Hispanic White; NLC, nanostructured lipid carriers; NP, nanoparticle; Nrf2, nuclear factor erythroid 2-related factor 2; OR, odds ratio; PD-1, programmed cell death protein-1; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; RR, relative risk; SLN, solid lipid nanoparticles; TIMP, tissue inhibitor of metalloproteinase; WPI, whey protein isolate

Key words: lycopene, cancer, synergism, delivery systems, epidemiology

Contents

1. Introduction

Cancer is a major challenge in the global public health field, and its morbidity and mortality rates continue to rise. According to the International Agency for Research on Cancer, ~20 million new cases of cancer alongside ~10 million cancer-related deaths were observed in 2022 and it has been predicted that there will be >35 million new cases by 2050 (1,2). It has been identified that family history, environment and lifestyle, and bacterial/viral infections are the main risk factors for cancer (1,3). Currently, natural product interventions such as lycopene and curcumin have become important strategies for cancer prevention and treatment, as most of these products are derived from vegetables, fruits and plants (4-7).

Lycopene, commonly referred to as 'plant gold', is a naturally occurring carotenoid mainly found in plants such as tomato, pink guava and watermelon, which provides them with a distinctive red color (Fig. 1) (8). Lycopene has been identified as an A-grade nutrient by the Food and Agriculture Organization, the Joint Expert Committee on Food Additives and the World Health Organization (9). The molecular formula of lycopene is $C_{40}H_{56}$, with 11 linear conjugated and 2 non-conjugated double bonds. This unique structure determines its strong antioxidant activity, such as quenching singlet oxygen, scavenging free radicals and inhibiting lipid peroxidation, which are associated with its notable health-promoting function (9,10). Moreover, these double bonds are sensitive to light, temperature and chemical reactions, which makes lycopene prone to isomerization (11). Notably, the bioavailability of cis-isomer is markedly higher compared with that of trans-isomer (12,13).

In recent years, individuals have become increasingly interested in lycopene due to its potential health benefits (Fig. 2). Specifically, epidemiological studies have reported that the intake and serum levels of lycopene are associated with a reduced risk of certain types of cancer, e.g., breast cancer (14,15). In addition, research has reported the synergistic effect of lycopene and chemotherapy drugs (e.g. docetaxel) or natural compounds (e.g. genistein) (16,17). Furthermore, a novel drug delivery system has previously been employed to improve its bioavailability to further increase its anticancer application (18).

The present review aimed to discuss the current developments that may improve lycopene efficacy in the prevention and treatment of cancer. This includes synergistic effects of lycopene with chemotherapy drugs or nutrients, novel drug delivery systems and relevant epidemiological studies to support the protective role of lycopene in cancer chemoprevention and treatment, and provide important reference value for further development and utilization of lycopene.

2. Safety and bioavailability of lycopene

Safety is an important issue to be considered for natural compounds. Several studies have evaluated the safety of different doses of lycopene, including acute toxicity studies, sub-chronic and chronic safety studies, reproductive studies and genetic toxicity studies (19,20). A total of ≤3 g/kg/day of different forms of lycopene (namely, lycopene extracted from tomatoes, synthetic lycopene and its crystalline extracts) are generally considered to be safe (21,22) and there has been no report of adverse events associated with the use of lycopene at a normal dose (≤3 g/kg/day) (23). The European Food Safety Authority panel derived an acceptable daily intake of 0.5 mg/kg body weight/day for animals based on a 'no-observed-adverse-effect level' for lycopene from all sources (24). Moreover, the US Food and Drug Administration has classed tomatoes and lycopene as 'Generally Recognized As Safe' (12,25). However, despite the absence of adverse effects with 150 mg/day intake of dietary or formulated lycopene in healthy individuals (26), it may be controversial to identify the intake as an 'Observed Safe Level' due to its short duration of use (one week) (20). Shao and Hathcock (20) proposed a 75 mg/day intake as the upper limit of lycopene for supplements, as no adverse effects were reported from continuous administration of 75 mg/day lycopene in a 4-week clinical study (27,28). Moreover, in several clinical studies, an intake of ≤30 mg/kg lycopene has been employed to generate chemopreventive and therapeutic effects (29-32). However, research has reported that high doses of lycopene supplementation (3.3 mg/kg /day, the equivalent dose to 45 mg/day in humans) and chronic alcohol ingestion can induce the expression of cytochrome CYP2E1 and may promote the harmful effects of excessive alcohol intake (e.g. a higher incidence of hepatic inflammatory foci was found in rats fed both alcohol and high dose lycopene group compared with the other groups) (33). Therefore, further research is warranted with a focus on individuals that consume high amounts of both alcohol and lycopene. Moreover, there have been case reports of lycopenemia which resulted in deep-orange discoloration of the skin due to daily intake of large amounts of tomato juice (180 ml-2 l for >10 years, and restriction of lycopene-containing foods was an effective method of treatment (34,35).

Lycopene is a hydrophobic compound and the presence of water can reduce its solubility and bioavailability (36,37). Moreover, lycopene naturally exists in fruits and vegetables in the form of a trans-isomer, which presents a low absorption rate and bioavailability (11). The bioavailability of lycopene is also influenced by cooking, interactions with other carotenoids and the presence of fat or oil (38). Thermal processing of tomato products can cause changes in the structure of lycopene to shift and yield cis-isomers in the product and this form is more bioavailable (36,39). The presence of fat in food also helps enhance the absorption of lycopene (40) and its absorption is influenced by the amount of ingested fat, and the type and emulsification of dietary fat (41,42). However, it has been recommended to avoid the consumption of lycopene concurrently with high dietary fiber, as several types of dietary fiber (e.g. pectin, guar, alginate, etc.) are associated with lower bioavailability of lycopene (43). In addition, genetic polymorphism also affects the bioavailability of lycopene, wherein a previous study suggested that specific single nucleotide polymorphisms (SNPs) of β-carotene oxygenase 1 (SNP rs6564851 in particular) are associated with greater effective lycopene uptake in humans (44). Currently, novel delivery systems have been developed to improve the bioavailability of lycopene, which are discussed in the present review.

3. Synergistic anticancer effects of lycopene with drugs or agents

Several studies have reported the anticancer effects of lycopene, which involve the inhibition of proliferation of cancer cells mainly through antioxidant activity, regulation of anti-inflammatory, growth factor signaling and apoptosis induction (4,11,22). By regulating these physiological processes, anticancer effects are exerted by modulating signaling pathways and their crosstalk (Fig. 3). As a natural compound, lycopene has notable advantages such as low toxicity, easy availability and low cost (4,44). In addition to exhibiting antitumor activity when used alone (45), lycopene in combination with other drugs (e.g. docetaxel, enzalutamide, sorafenib) can also enhance anticancer effects or reduce side effects caused by cancer treatment (Table I).

Synergistic efficacy with chemotherapeutic drugs. In the treatment of prostate cancer, the addition of lycopene was reported to enhance the growth-inhibitory effect of docetaxel more effectively on DU145 cells with insulin-like growth factor (IGF)-1 receptor (IGF-1R) high expression compared with that on prostate cancer cell lines with IGF-1R low expression (46). The present research also reported that docetaxel plus lycopene was associated with tumor regression with a 38% increase in antitumor efficacy *in vivo*. Mechanistically, lycopene inhibited IGF-1R activation through inhibiting IGF-1 stimulation and by elevating the expression and secretion of IGF binding protein 3 (IGFBP3), as well as suppressed AKT kinase activity and survivin expression (46). This study also suggested that patients with castration-resistant prostate cancer (CRPC) with IGF-1R upregulation may benefit from the combination of docetaxel plus lycopene. Lycopene can also enhance the sensitivity of

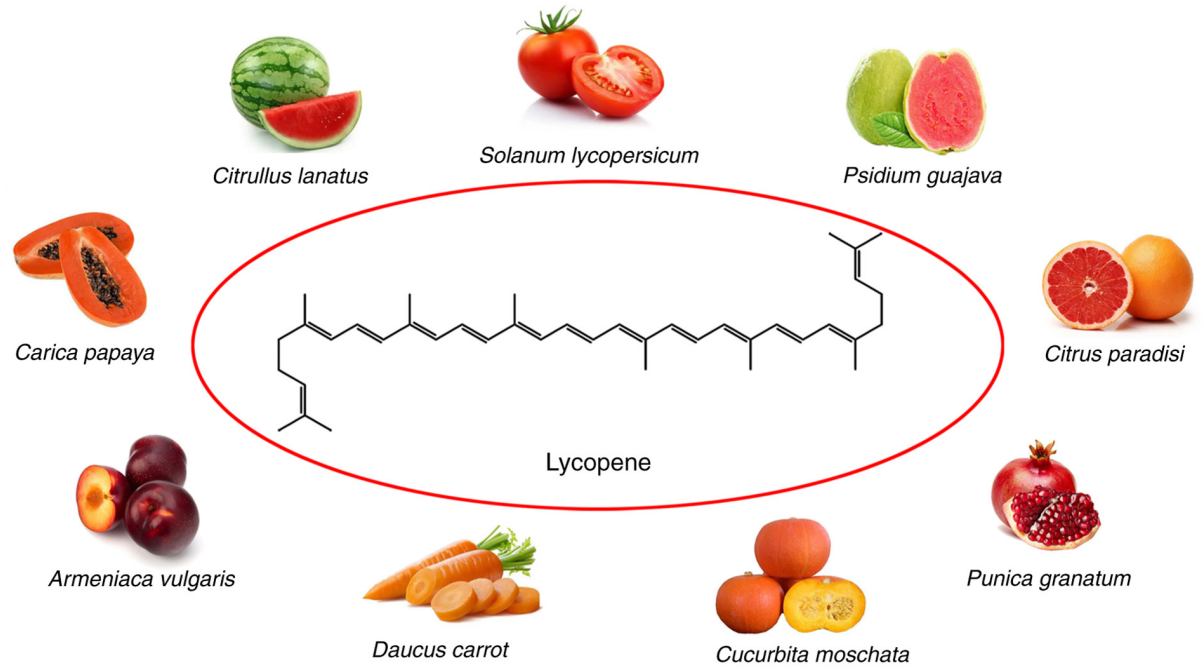

Figure 1. Main plant sources of lycopene.

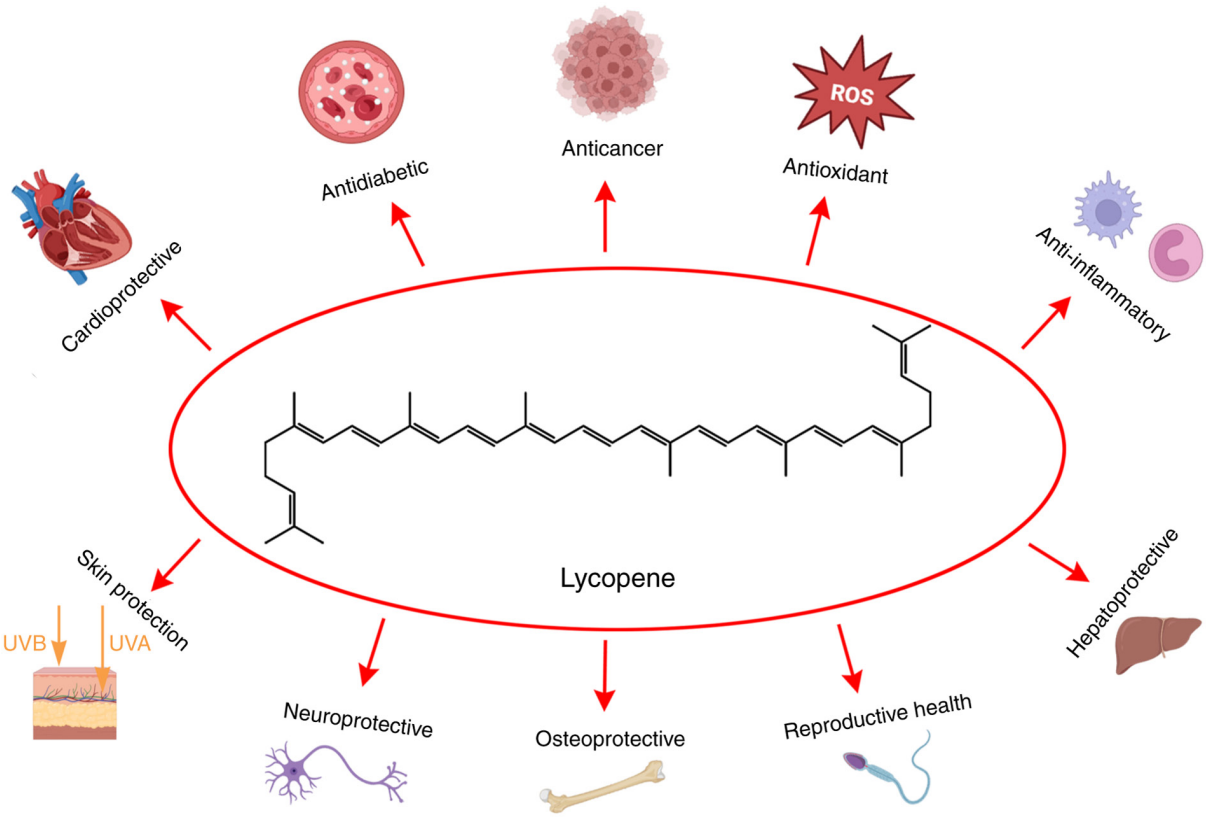

Figure 2. Biological effects of lycopene. ROS, reactive oxygen species; UV, ultraviolet. This figure was created with BioRender.com.

CRPC to enzalutamide (47). The combination of lycopene and enzalutamide can inhibit the expression of p-AKT, p-enhancer of zeste homolog 2, androgen receptor and proliferate cell nuclear antigen in 22RV1 and C4-2B cells, as well as prohibit CRPC bone metastasis *in vivo*, which provides novel therapeutic strategies that can delay the progression of patients with CRPC (47). The combination application of sorafenib and lycopene also demonstrated an additional effect of reducing the number of metastatic tumors in the lung, mechanistically due to the inhibition of MAPK signaling pathway and a decrease in the matrix metalloproteinase (MMP)-2 and MMP-9 activities via the activation of the nonmetastatic protein 23 homologue

Table I. Summary of synergism of lycopene with other chemicals for cancer prevention and treatment.

A, Chemotherapy drugs

First author/s, year	Compounds	Model	Dosage	Mechanism	(Refs.)
Tang *et al*, 2011	Docetaxel	*In vitro*, *in vivo*	1 μM; 15 mg/kg	Inhibition of IGF-1R activation via inhibition of IGF-1 stimulation, which elevated the expression levels of IGFBP3, as well as suppression of AKT kinase activity and survivin expression.	(46)
Chen *et al*, 2022	Enzalutamide	*In vitro*, *in vivo*	15 μM; 15 mg/kg	Inhibition of the expression of p-AKT, EZH2 and PCNA in 22RV1 and C4-2B cells, as well as prohibition of CRPC bone metastasis *in vivo*.	(47)
Chan *et al*, 2022	Sorafenib	*In vivo*	2 mg/kg; 5 mg/kg	Inhibition of MAPK signaling pathway and decreased MMP-2 and MMP-9 activities through the activation of NM23-H1, TIMP-1 and TIMP-2 expression.	(48)
El-Masry *et al*, 2024	Sorafenib	*In vitro*, *in vivo*	20-180 μM; 20 mg/kg	Targeting autophagy, apoptosis and suppression of proliferation, with a notable decrease in the TNF-α and VEGF gene expression levels and a marked increase in caspase 3 gene expression levels. Reshaping inflammatory markers of IL-1β.	(49)
Alhoshani *et al*, 2022	5-FU	*In vitro*	60, 90 and 120 μg/ml	Improvement in the antioxidant parameters of SOD and GSH levels, and increase in the IFN-γ expression levels to further enhance the cancer killing effect of 5-FU.	(50)
Aktepe *et al*, 2021	Cisplatin	*In vitro*	10 μM	Elevation of Bax expression levels, decrease of Bcl-2 expression levels, inhibition of NF-κB-mediated inflammatory responses and modulation of Nrf2-mediated oxidative stress.	(51)
Holzapfel *et al*, 2017	Paclitaxel carboplatin	*In vivo*	15 mg/kg	Reduction of the intraperitoneal metastatic load and decrease in the expression levels of ITGA5, ITGB1, MMP-9, ILK and FAK.	(52)
Jiang *et al*, 2019	Anti-PD-1	*In vivo*	40 mg/kg	Elevation of IL-1 and IFN-γ, and decrease of IL-4 and IL-10 expression levels.	(53)
Pan *et al*, 2022	Cyclophosphamide	*In vivo*	5, 10 and 20 mg/kg	Increase in the expression levels of SOD, GSH, sIgA, IL-1β, IL-4, IL-6, IL-12, IFN-γ and TNF-α, decreased MDA and NO, and upregulation of the expression levels of TLR4, MyD88, TRAF6, TRIF, p-P38 p38 and NF-κB p65.	(58)
Zhu *et al*, 2020	Doxorubicin	*In vivo*	3 mg/kg	Decrease in the expression levels of MDA, CK and LDH, and increase in the expression levels of GSH.	(59)
Sahin *et al*, 2010	Cisplatin	*In vivo*	6 mg/kg	Increase in the expression levels of Nrf2/HO-1, CAT, GPx and SOD, and reduced inflammation by restraining NF-κB p65.	(60)
Turk *et al*, 2011	Cisplatin	*In vivo*	10 mg/kg	Suppression of lipid peroxidation and improvement of germ apoptosis.	(61)

Table I. Continued.

A, Chemotherapy drugs

First author/s, year	Compounds	Model	Dosage	Mechanism	(Refs.)
Preet *et al*, 2013	Quinacrine	*In vitro*	2-10 μM	Promotion of apoptosis and decreased levels β-catenin, cyclin D1 and increased levels of APC.	(64)

B, Natural compounds or nutrients

First author/s, year	Compounds	Model	Dosage	Mechanism	(Refs.)
Sahin *et al*, 2011	Genistein	*In vivo*	20 mg/kg	Decrease in the expression levels of MDA, 8-isoprostane and 8-OhdG. Decreased Bcl-2 expression and markedly increased Bax, caspase 3 and caspase 9 expression levels.	(17)
Langner *et al*, 2019	Sulforaphane, quercetin and curcumin	*In vitro*	2 μM	Inhibition of colon cancer cells proliferation.	(56)
Linnewiel-Hermoni *et al*, 2015	Phytoene phytofluene/ β-carotene/ astaxanthin/ retinoic acid	*In vitro*	0.3 μM	Inhibition of the androgen receptor activity and activation of the EpRE/ARE system.	(57)
Moselhy *et al*, 2008	Melatonin	*In vivo*	50 mg/kg	Elevation of the expression levels of SOD, CAT, GPx, reduction of NO and MDA.	(65)
Limpens *et al*, 2006	Vitamin E	*In vivo*	5 mg/kg	Suppression of orthotopic growth of PC-346C prostate tumors by 73% and increase in median survival time by 40%.	(66)
Tang *et al*, 2012	Fish oil	*In vivo*	3 and 6 mg/kg	Suppression of MMP-7, MMP-9, COX-2 and PGE_2.	(67)
Velmurugan *et al*, 2005	S-Allylcysteine	*In vivo*	1.25 mg/kg	Diminished lipid peroxidation by increasing GSH and GSH-dependent enzymes.	(68)
Al-Malki *et al*, 2012	Tocopherol	*In vivo*	50 mg/kg	Decrease in the levels of MDA and NO, and increase in the levels of SOD, CAT and GPx.	(69)

5-FU, 5-fluorouracil; 8-OhdG, 8-hydroxy-2'-deoxyguanosine; APC, adenomatous polyposis coli; CAT, catalase; CK, creatine kinase; CRPC, castration-resistant prostate cancer; COX-2, cyclooxygenase-2; EZH2, enhancer of zeste homolog 2; EpRE/ARE, electrophile/antioxidant response element; FAK, focal adhesion kinase; GPx, glutathione peroxidase; GSH, glutathione; HO-1, heme oxygenase-1; IFN, interferon; IGF-1R, insulin-like growth factor-1 receptor; IGFBP3, IGF binding protein 3; ILK, integrin-linked kinase; ITGA5, integrin α5; ITGB1, integrin β1; LDH, lactate dehydrogenase; MDA, malondialdehyde; MMP, matrix metalloproteinase; MyD88, myeloid differentiation primary response gene 88; NM23-H1, nonmetastatic protein 23 homologue 1; NO, nitric oxide; Nrf2, nuclear factor erythroid 2-related factor 2; PCNA, proliferating cell nuclear antigen; PD-1, programmed cell death protein-1; SOD, superoxide dismutase; TIMP, tissue inhibitor of metalloproteinase; TRAF6, TNF receptor associated factor 6; TRIF, toll/IL-1receptor domain-containing adaptor protein inducing IFN-β; VEGF, vascular endothelial growth factor.

1, tissue inhibitor of metalloproteinase (TIMP)-1 and TIMP-2 expressions (48). The combination of sorafenib with lycopene is also a valuable therapy for solid Ehrlich carcinoma (49). The combination therapy was reported to be superior compared with sorafenib or lycopene alone in causing early cell cycle arrest, which suppressed the viability of cancer cells and increased apoptosis and autophagy. Similarly, the combination therapy exhibited a marked decrease in TNF-α and VEGF gene expression, whereas a notable increase in caspase 3 gene expression levels was observed. Furthermore, the combined treatment led a reduction of inflammation, which manifested in reshaping inflammatory markers of IL-1β. The results of

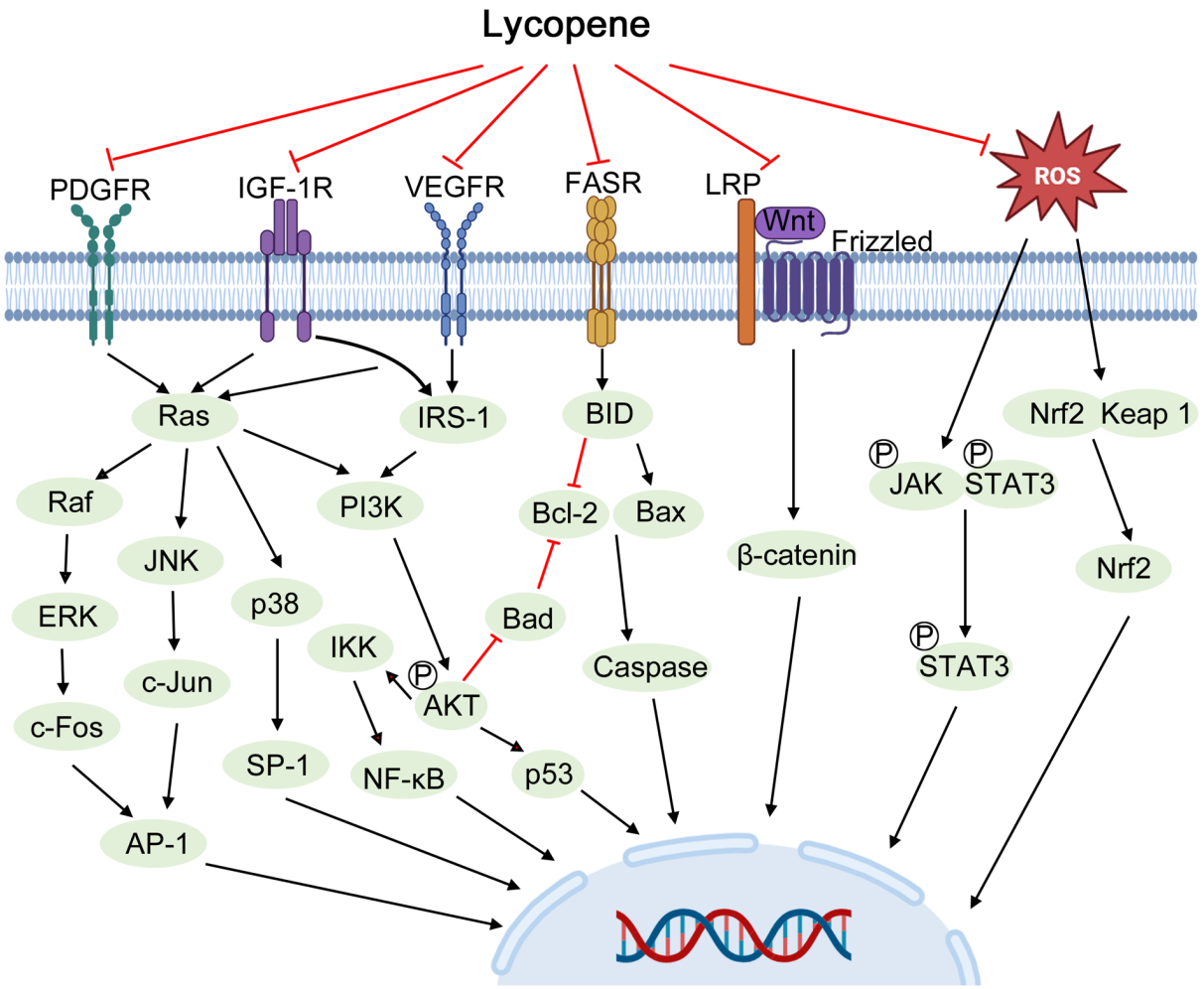

Figure 3. Main anticancer mechanism of lycopene. This figure was created with BioRender.com. The red lines represent inhibitory effects and the black lines activation effect. ROS, reactive oxygen species; P, phosphorylation; AP-1, activator protein 1; BID, BH3 interacting domain death agonist; c-Fos, cellular FBJ osteosarcoma viral oncogene homolog; FASR, Fas receptor; JAK, janus kinase; IGF-1R, insulin-like growth factor-1 receptor; IRS-1, insulin receptor substrate-1; Keap1, kelch-like ECH-associated protein 1; LRP, low-density lipoprotein receptor-related protein; Nrf2, nuclear factor erythroid 2-related factor 2; PDGFR, platelet-derived growth factor receptor; SP-1, specificity protein-1.

the aforementioned studies indicate that the combination of sorafenib with lycopene demonstrates potential as a cancer therapy in the future.

During therapy with 5-fluorouracil (5-FU) on Caco2 cells, lycopene supplementation was reported to improve antioxidant parameters such as superoxide dismutase and glutathione (GSH) levels and increase IFN-γ expression to further enhance the anticancer effect of 5-FU (50). Lycopene was reported to sensitize the cervical cancer cells to cisplatin therapy. The inhibitory effect of cisplatin was enhanced with lycopene addition by reducing the cell viability to 37.4% compared with 65.6 and 71.1% of lycopene and cisplatin treatment alone, respectively (51). Lycopene treatment markedly elevated Bax expression and depressed Bcl-2 expression. The anticancer effect of lycopene may also be associated with inhibition of NF-κB-mediated inflammatory responses, and modulation of nuclear factor erythroid 2-related factor 2 (Nrf2)-mediated oxidative stress (51). Due to the disruption of the redox homeostasis of cancer cells, lycopene affects reactive oxygen species levels by simulating the production of detoxification/antioxidant enzymes, (e.g. superoxide dismutase, catalase, glutathione-S-transferase) which thereby promote the preferential targeting of cancer cells by the antioxidant activity of lycopene, whilst sparing normal tissues. Research has also demonstrated that prophylactic administration of lycopene can also markedly reduce the intraperitoneal metastatic load and when given as a therapeutic use, it can notably reduce the tumor load of ovarian cancer-bearing mice (52). Moreover, lycopene has been reported to synergistically enhance the response of ovarian cancer cells to paclitaxel and carboplatin, which was associated with a reduction in the expression levels of integrin α5 (ITGA5) and inhibition of ERK1/2, which activated MAPK signaling (52).

Lycopene can also enhance the antitumor efficacy of immune checkpoint inhibitors (53). Combining lycopene and anti-programmed cell death protein (PD)-1 therapy was reported to reduce tumor volume and weight and enhance cell apoptosis, and elevate IL-1 and IFN-γ levels, whilst decreasing the expression levels of IL-4 and IL-10 (53). Moreover, lycopene treatment was also reported to increase the $CD4^+/CD8^+$ ratio in the spleen and promote IFN-γ-expressing $CD8^+$ T cells in tumor tissues. Lycopene also reduced the methylation levels of interferon regulatory factors (IRF)1 and IRF7 promoters to promote IFN-γ expression. Notably, under IFN-γ

stimulation, lycopene reduced the expression of PD-ligand (L)1 by activating JAK and inhibiting AKT phosphorylation. In addition, lycopene may synergize with anti PD-1 therapy to downregulate tumor-intrinsic PD-L1 signaling and expression by decreasing IGF-1R expression to inactivate both the PI3K/AKT and Raf/MEK/ERK pathways (54).

Synergistic efficacy with other natural compounds or nutrients. Genistein is a natural compound with potential anti-breast cancer activity. Previous research demonstrated that, when combined with lycopene, the incidence of breast cancer was reduced by ~60% compared with that of single use of genistein or lycopene of 40 and 30%, respectively (17). Furthermore, the proportions of adenocarcinoma masses were also reported to be decreased by the lycopene and genistein combination, which have been mechanistically associated with the reduction of oxidative stress, specifically reflected in the decrease of malondialdehyde (MDA), 8-isoprostane and 8-hydroxy-2'-deoxyguanosine levels. However, certain studies have reported that the combination of lycopene and soy isoflavones does not produce an additive effect in the treatment of patients with prostate cancer (55). A mixture of lycopene, sulforaphane, quercetin and curcumin also enhanced the antiproliferative effect of 5-FU and cisplatin in colon cancer cells, and had no effect on DNA synthesis in normal colon epithelial cells (56). The combination of lycopene and phytoene phytofluene/β-carotene/astaxanthin/retinoic acid exhibited notable synergistic effect, whilst the use of lycopene alone had no effect on LNCaP cells. However, at the same concentration, when combined with the other aforementioned compounds, it demonstrated inhibitory effects on cell growth and this effect was associated with the inhibition of androgen receptor activity and activation of the electrophile/antioxidant response element system (57).

Alleviating the toxicity of chemotherapy drugs. The combination of lycopene and chemotherapy drugs can not only improve efficacy but also alleviate adverse reactions (58-61). Cyclophosphamide, as a first-line chemotherapy drug for cancer in clinical practice, can cause severe intestinal toxicity and affect the treatment effect and prognosis of patients (58). The combined use of lycopene could improve the situation through the following mechanisms: Regulating the gut-liver axis; repairing the intestinal mucosal barrier; activating the toll-like receptor 4-myeloid differentiation primary response gene/toll/IL-1receptor domain-containing adaptor protein inducing the IFN-β-TNF receptor associated factor 6 signaling pathway to activate the intestinal tract; restoring the diversity of intestinal microbiota; inhibiting the oxidative damage and inflammatory response caused by the transfer of harmful bacteria to the liver; and; serving a preventive role in intestinal immune damage induced by cyclophosphamide (58). Doxorubicin, as a broad-spectrum anticancer drug, is known for its adverse reaction of cardiotoxicity (59). Zhu *et al* (59) developed lycopene-loaded liposomes (L-LYC) to evaluate its synergistic effect with doxorubicin against its cardiotoxicity. Compared with single use doxorubicin, the combination of L-LYC and doxorubicin demonstrated markedly increased cytotoxicity *in vitro* and decreased the tumor size in B16 melanoma-bearing mice *in vivo*, as well attenuated the cardiotoxicity induced by doxorubicin by decreasing the levels of creatine kinase, lactate dehydrogenase, MDA and increasing GSH to prevent the leakage of cardiac enzymes. Cisplatin is used to treat several types of solid tumors (e.g. lung cancer, nasopharyngeal carcinoma, bladder cancer) and is a common chemotherapeutic drug in clinics; however, it has notable adverse reactions (62). For example, ~25-35% of patients experience a marked decrease in renal function after the use of cisplatin. Sahin *et al* (60) reported that a lycopene complex (containing 6% lycopene, 1.5% tocopherols, 1% phytoene and phytofluene, and 0.2% β-carotene) could attenuate cisplatin-induced nephrotoxicity by modulating Nrf2/heme oxygenase-1 signaling and reducing inflammation by restraining NF-κB p65. Reproductive toxicity caused by cisplatin is also a matter of concern (63). However, lycopene has been reported to prevent testicular apoptosis induced by cisplatin through suppression of lipid peroxidation and germ cell apoptosis (61).

The above studies and several other studies (64-69) on the synergistic effects of enhancing anticancer activity have reported that the combination of lycopene with drugs or nutrients has notable synergistic effects. However, current research mostly involves cell line and animal-model studies, and the mechanistic research is not deep enough. In addition, the number of subjects enrolled in clinical studies are relatively small, large-scale, multicenter clinical studies are warranted to provide real-world data to support the synergistic effects of lycopene.

4. Advanced nanotechnology delivery systems to enhance the anticancer activity of lycopene

Due to its insolubility in aqueous solvents, lycopene exhibits low bioavailability and stability, which limits its application in cancer treatment (44). To overcome these limitations, researchers have used several delivery systems to load lycopene to improve bioavailability and enhance pharmacokinetic properties (70), and these delivery systems were mainly nanotechnology-based. The use of nanocarriers can promote controlled delivery of drugs to specific target sites without altering their biological activity and pharmacological properties, improving the stability and solubility of lipophilic and hydrophilic bioactive substances in several types of media, which expands the potential of lycopene for drug applications in therapy (71,72). Currently, the use of nanocarriers to encapsulate lycopene mainly involves organic nanosystems based on lipid nanostructures, such as solid lipid nanoparticles (SLN), nanostructured lipid carriers (NLC) and niosomes (NIs).

SLN consist of crystalline lipid matrix that are solid at room temperature and certain tension agents (e.g. poloxamer) enable them to accommodate molecules between the fatty acid chains in the lipid core or surface (73,74). The main advantage of SLN is the use of solid lipids, which reduce the fluidity of drugs in the matrix, prevent particle aggregation, improve stability and enable sustained drug release. Moreover, when administered orally, SLN are absorbed by the reticuloendothelial system and bypass the first-pass metabolism, which thereby increases the bioavailability of drugs (75). Jain *et al* (76) applied a homogenization-evaporation technique to loaded lycopene with SLN with different ratios of biocompatible *viz*. compritol

ATO 888 and gelucire and evaluated their effect on MCF-7 cells. Compared with free lycopene, a notably higher cellular uptake of lycopene-SLNs was reported in MCF-7 cells and lycopene-SLN markedly decreased the concentration and time dependent cell survival of MCF-7 cells. Moreover, the combination of lycopene-SLNs and methotrexate notably enhanced anticancer activity. NLC is an enhanced carrier of SLN, which replaces certain solid lipids with liquid lipids to form mixed lipids, and maintains them in a solid state at room temperature and body temperature (77,78). Singh *et al* (79) developed an optimized NLC of lycopene with the encapsulation efficiency and drug loading of 84.5 and 54.0%, respectively, for efficient absorption. Results from *ex vivo* gastrointestinal tract permeation studies demonstrated lycopene loaded in NLC can enhance the permeation ~4-fold increase in the serosal medium and inhibit P-glycoprotein efflux pump, which aided in the permeation of lycopene through the intestinal milieu for improved absorption (79). Furthermore, lycopene-NLC exhibited strong cytotoxicity against human breast cancer cells (79). As lipid drug carriers, SLN and NLC are widely studied and have the advantage of a relatively simple preparation method and notable encapsulation efficiency and drug loading rate, which should be explored in future research (Table II).

Polymeric nanoparticles (NPs) are composed of encapsulated drugs and polymer excipients, and the surface properties of NPs can be modified by using different polymer end groups or attaching polymers to the surface of NPs (80,81). Targeted ligands, such as antibodies, peptides can also attach to NPs surfaces to allow for specific interactions with tissue components or cell receptors (82,83). Bano *et al* (84) synthetized thermosensitive polyethylene glycol (PEG)-poly(N-isopropylacrylamide) (PNIPAAM)-PEG-based co-polymeric nanoparticles to encapsule of lycopene and evaluate their *in vitro* anticancer activity and inhibitory effect on 12-O-tetradecanoylphorbol-13-acetate-promoted skin inflammation and tumorigenesis in Swiss albino mice. Higher doses of PNIPAAM-PEG-lycopene were reported to reduce the percentage of mice bearing tumors to 4.1±0.91 with a 41.4% incidence compared with that of 12.7.4±1.31 with a 97.3% incidence in the model group, which markedly reduced the incidence rate and tumor burden of skin tumors (84). This effect was associated with the inhibition of cyclooxygenase-2, oxidative stress response and the induction of apoptosis. Lycopene loaded with NPs increases aqueous solubility and bioavailability of lycopene, which makes it a promising strategy for the treatment of skin inflammation.

Moreover, whey protein isolate (WPI), a type of amphiphilic material and the semitransparent liquid portion of milk, is obtained by removing the curd after coagulation. WPI is a highly bioavailable protein composed of vitamins and minerals and rich in essential and branched chain amino acids (85,86). WPI can intercept hydrophobic substances superior to commonly used carriers of the same type. Moreover, it is easy to digest and unload its contents under normal gut conditions (87,88). Jain *et al* (89) developed a novel strategy of formulating lycopene-loaded WPI nanoparticles (lycopene-WPI-NPs) solely using the rational blend of biomacromolecule without the use of equipment-intensive techniques. As lycopene-WPI-NPs can maintain the plasma level of lycopene for a long time, it demonstrated stronger antitumor characteristics against breast cancer compared with free lycopene and in subsequent survival tests, lycopene-WPI-NPs exhibited a superior animal survival rate.

Nanoemulsions are oil-in-water, water-in-oil dispersions stabilized by two immiscible liquids with appropriate surfactants (90,91). Huang *et al* (92) prepared a lycopene-nanogold nanoemulsion containing Tween 80 as an emulsifier. The nanoemulsion resulted in a 15-fold rise in early apoptotic cells of HT-29 compared with untreated cells, and markedly decreased the expressions of procaspases 8, 3 and 9, as well as poly-ADP ribose polymerase-1 and Bcl-2, whereas an increase in Bax expression was observed. The nanoemulsion was also associated with an upregulation of the epithelial marker, E-cadherin, and downregulated AKT, NF-κB, pro-MMP-2 and active MMP-9 expressions to reverse the invasion-associated markers. Furthermore, the lycopene-nanogold nanoemulsion may hold potential in colorectal cancer (CRC) therapy (92).

Unmodified nanocarriers often fail to achieve specific targeting and efficient antigen presentation (82,83). Therefore, improving their active targeting and stability, and prolonging *in vivo* circulation time, has become a research hotspot in drug delivery systems. In recent years, the development of several engineered nanocarriers has overcome the aforementioned shortcomings. NI is a new generation of vesicular nanocarriers and provides a multi-lamellar carrier for lipophilic and hydrophilic bioactive substances in the self-assembled vesicle (93). As an alternative to liposomes, NI is considered more chemically and physically stable, especially stable at 25-37˚C (94). Kusdemir *et al* (95) synthesized prostate-specific membrane antigen (PSMA)-targeted NI using a thin-film hydration method followed by bath sonication. Drug-loaded NI [lycopene-indocyanine green (ICG)-NI] were coated with DSPE-PEG-COOH and subsequently anti-PSMA antibodies conjugated to NI (lycopene-ICG-NI-PSMA). The encapsulation efficiency was 45 and 65% upon dual encapsulation of ICG and lycopene, respectively. In *in vitro* experiments, lycopene-ICG-NI-PSMA selectively increased the anti-proliferative and anti-apoptotic effects on PSMA + LNCaP cells, with a lycopene-ICG-NI uptake rate of 25.67% and a lycopene-ICG-NI-PSMA uptake rate of 41.12% in LNCaP cells, demonstrated the targeted NI displayed improved cellular association and decreased cell viability of prostate cancer cells (95). Evidence showed that the expression of IGF-1R is activated in breast cancer, and its activation through IGF-1 signaling pathway leads to impaired tumor cell proliferation, apoptosis, increased survival rate and resistance to cytotoxic therapeutic drugs (18,96). Thus, Mennati *et al* (18) loaded lycopene and IGF-1R-small interfering (si)RNA into methoxypoly (ethylene glycol)-poly(caprolactone) hybridized with dimethyldioctadecylammonium bromide cationic lipid nanoparticles to simultaneously deliver lycopene and IGF-1R-siRNA to MCF-7 breast cancer cells. The results demonstrated that the co-delivery of lycopene and IGF-1R-siRNA markedly prevented the growth and proliferation of MCF-7 cells, indicating it may be an effective strategy for the treatment of cancer; however, this study lacked *in vivo* experiments to confirm this effect.

Moreover, although the development of novel delivery systems provides a potential effective approach for the

Table II. Advanced nanotechnology delivery systems for the improvement of bioaccessibility and bioavailability of lycopene against cancer.

Nanocarrier	Incorporation method	EE, %	DL, %	Drug release kinetics/stability	Bioaccessibility/bioavailability enhancement	(Refs.)
SLN	Lycopene was loaded into SLN by adding 10 mg lycopene with lipid in organic dispersion phase. Non-incorporated lycopene was removed through cellulose dialysis bag. The suspension was filtered (0.45 mm membrane filter) to remove excess lipid.	79.60±2.90	13.96±0.98	A biphasic release pattern of initial rapid followed by slow and sustained release. At the end of 8 h, >30% lycopene was released. Following a 96-h incubation, 90.4±3.7% lycopene was released.	Enhanced cytotoxicity in MCF-7 breast cancer cells. The higher efficacy of lycopene-SLNs was associated to marked uptake in the cells. Notable adjunct effect with methotrexate.	(76)
NLC	Solid lipid Precirol ATO 5 and liquid lipid vitamin E were heated and under stirring and lycopene (oil phase) was added. At the same time Tween 80 and polaxamer 188 (1:2) was heated at the same temperature. This hot surfactant solution was dispersed in the oil phase dropwise under continuous stirring, then the obtained pre-dispersion was ultrasonicated. After cooling down to room temperature the lycopene-NLC dispersion was obtained.	84.50±4.38	54.00±2.65	Lycopene-NLC exhibited a burst drug release pattern during its initial stage following a sustained release over 48 h with a cumulative drug release of 82.33±3.67%. During the storage period at the different time interval for 90 days, the lycopene-NLC demonstrated no precipitate formation, no phase separation and good dispersibility.	*Ex vivo* gut permeation studies demonstrated ~4-fold increase in the permeation of lycopene loaded NLC. Enhanced cytotoxicity in MDA-MB.231 breast cancer cells.	(79)
Polymeric NPs	Lycopene was physically entrapped inside the hydrophobic	>85	Not available	A sustained release of lycopene from the nanopolymer at a physiological pH of	Nanolycopene demonstrated stronger antioxidant activity and comparable *in vitro* anticancer efficacy with free	(83)

Table II. Continued.

Nanocarrier	Incorporation method	EE, %	DL, %	Drug release kinetics/stability	Bioaccessibility/bioavailability enhancement	(Refs.)
	core of the polymeric micelles after the complete polymerization reaction. 50 mg lyophilized powder was dispersed in 10 ml double-distilled water and stirred to reconstitute the micelles. Subsequently, the drug solution in DMSO was gradually added in the co-polymeric solution and stirred till no more settling of the drug occurred.			7.4 in phosphate buffer.	lycopene against the melanoma cell line B16. Markedly reduced the incidence rate and tumor burden of skin tumors by reducing the percentage of mice bearing tumors to 4.1±0.91 with a 41.4% incidence compared with that of 12.7.4±1.31 with a 97.3% incidence in the model group.	
NPs	WPI (8% w/v) was dispersed in deionized water, the pH was adjusted to 8, after stirred for 1 h and kept at 4˚C overnight for complete hydration of biopolymer. Ethanol-containing lycopene (5 mg/ml) was added into the protein solution in a dropwise manner and at a rate of 1 ml/min under continuous stirring at 40˚C. Instantaneously after desolvation using ethanol, 10% genipin in	53.70-64.70	8.20-2.30	The lycopene-WPI-NPs formulations demonstrated biphasic release pattern *viz* initial rapid followed by slow and sustained release up to 24 h. At physiological pH (7.4), ~75% of lycopene was released from NPs within 8-h incubation. The average particle size, particle size distribution and EE of lycopene-WPI-NPs demonstrated no notable changes upon storage for 3 months.	Lycopene-WPI-NPs exhibited notable cancer prevention and anticancer activity. With lycopene-WPI-NPs formulation, animal survival (100%) was notably improved compared with that of free lycopene (66.67%) and negative control group (16.67%).	(89)

Table II. Continued.

Nanocarrier	Incorporation method	EE, %	DL, %	Drug release kinetics/stability	Bioaccessibility/bioavailability enhancement	(Refs.)
	water was added to facilitate particle crosslinking and this process was performed whilst stirring the dispersion over a period of 24 h.					
NPs	The nanoprecipitation method was used to prepare mPEG-PCL-DDAB nanocarriers. The copolymer (mPEG-PCL)/ lycopene in acetone was added dropwise to the mixture of the DDAB/ deionized water mixture to form LNP. According to the formula, certain amounts of LNP must be combined with the optimum dose of siRNA and incubated at room temperature for 60 min to obtain LNPsiRNA.	99.7	Not available	Not available	The formulation exhibited dual delivery of IGF-1R-siRNA and lycopene, which notably induced the process of apoptosis and arrested cell cycle in the MCF-7 tumor cell lines.	(18)
Nanoemulsion	The lycopene-nanogold nanoemulsion was prepared by mixing 1.7 mg lycopene with 1.2 g Tween 80, which was stirred manually for homogeneity. Subsequently, 7.6 ml gold nanoparticles (3-5 nm, 80 ppm)	~80	Not available	High stability with no notable difference in particle size (19.5-20.5 nm) was observed for the lycopene-nanogold nanoemulsion samples stored at 4˚C and 25˚C for 3 months or heated at 100˚C for 4 h. A minor change in the level of lycopene was reported when	Nanoemulsion treatment demonstrated a 15-fold rise in early apoptotic HT-29 cells. A reduction of ·~90% procaspase 3 and 8 levels, 98% reduction of procaspase 9, as well as 95% reduction of Bcl-2 was observed after nanoemulsion treatment in HT-29 cells. Nanoemulsion markedly decreased the migration rate of HT-29 cells. A possible passive targeting effect may exist.	(92)

Table II. Continued.

Nanocarrier	Incorporation method	EE, %	DL, %	Drug release kinetics/stability	Bioaccessibility/bioavailability enhancement	(Refs.)
	were added, followed by deionized water, then sonicated for 1 h to obtain lycopene-nanogold nanoemulsion (12 ml) with a final lycopene and gold concentration of 141.6 and 51.0 μg/ml, respectively.			the nanoemulsion samples were stored at a pH of 2.0, 3.5, 6.0, 6.8 and 7.4 for 1, 2, 4, 6, 12 or 24 h.		
NI	Lycopene-loaded NIs were synthesized using the thin-film hydration method followed by bath sonication. A total of 0.47 mM lycopene was dissolved in the organic solvent and 0.038 mM ICG was added to the dried lipid film before the agitation step. Subsequently, 0.4 μmol DSPE-PEG-COOH was dissolved in lycopene-ICG-NI dispersion and stirred for 2 h to obtain PEGylated Nis (lycopene-ICG-NI-PEG). Anti-PSMA antibodies were conjugated to lycopene-ICG-NI-PEG via the EDC/NHS method by producer method to obtain	65.29±7.21	Not available	The formulations demonstrated biphasic release pattern for lycopene. A burst release of lycopene after 1 h of incubation at 37˚C. In total, 69.09% of entrapped lycopene was released to the medium at the end of the time scale.	Lycopene-ICG-NI markedly reduced cell viability for PC-3 and LNCaP cells. Lycopene-ICG-NI-PSMA decreased cell viability slightly in PC-3 cells, compared with that of lycopene-ICG-NI, to 50.2% in LNCaP cells. In a fluorescence incorporation study, lycopene-ICG-NI-PSMA exhibited a marked increase in uptake in LNCaP cells compared with lycopene-ICG-NI (41.12 vs. 25.67%).	(95)

Table II. Continued.

Nanocarrier	Incorporation method	EE, %	DL, %	Drug release kinetics/stability	Bioaccessibility/bioavailability enhancement	(Refs.)
	lycopene-ICG-NI-PSMA.					

DSPE, 1,2-distearoyl-sn-glycero-3-phosphoethanolamine; DDAB, dimethyldioctadecylammonium bromide; DL, drug loading; EDC, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide; EE, encapsulation efficiency; ICG, indocyanine green; IGF-1R, insulin-like growth factor-1 receptor; LNP, lycopene-encapsulated mPEG-PCL-DDAB nanoparticle; NHS, N-hydroxysuccinimide; NI, niosome; NLC, nanostructured lipid carrier; NPs, nanoparticles; PCL, polycaprolactone; PEG, polyethylene glycol; PSMA, prostate-specific membrane antigen; siRNA, small interfering RNA; SLN, solid lipid nanoparticles; WPI, whey protein isolate.

application of lycopene, several novel formulations (e.g. exosomes) have not been fully utilized to improve the effectiveness of lycopene and certain delivery system studies have only been performed at the *in vitro* stage, lacking evidence from *in vivo* studies. The above studies have also only investigated the effectiveness of the novel carriers loaded with lycopene, which lack research on their mechanisms of action. Additionally, although nanomaterials have driven advances in medicine, their toxicity and potential risks are also notable (97). To the best of our knowledge, no nanotechnology delivery systems loaded with lycopene have been approved for marketing to date. Therefore, animal model and epidemiological studies are necessary to provide further evidence for the use of lycopene in the treatment of cancer.

5. Lycopene in anticancer epidemiological studies

Prostate cancer. Prostate cancer ranks as the most frequently diagnosed cancer in men (1). In a prospective study, it was reported that higher lycopene intake was inversely associated with total prostate cancer and had a greater association with mortality from prostate cancer [top compared with bottom quintile; hazard ratio (HR), 0.72; 95% CI, 0.56-0.94; P=0.04)] (98). Additionally, in a restricted population of screened participants, the inverse association was significantly stronger compared with total participants for mortality from prostate cancer (HR, 0.47; 95% CI, 0.29-0.75; P=0.009) (98). The study also indicated that an early intake, but not recent intake, of lycopene was inversely associated with prostate cancer. Moreover, a cross-sectional study from the National Health and Nutrition Examination Survey (2003-2010) indicated that an insufficient lycopene intake (who consumed zero lycopene or <8,000 μg/day from daily food) was associated with a high risk of prostate cancer (99). It was reported that ethnicity was the only factor that influenced lycopene intake from the daily diet: Non-Hispanic Black (NHB) men with prostate cancer consumed significantly less lycopene compared with non-Hispanic White (NHW) men (3.716 vs. 6.487 μg; P=0.01). Furthermore, sufficient lycopene intake (intake from daily food as ≥8,000 μg) significantly reduced the risk of prostate cancer [odds ratio (OR), 0.40; 95% CI, 0.18-0.85; P=0.02]. In addition, NHB men had a significantly higher risk of prostate cancer compared with NHW men (OR, 2.27; 95% CI, 1.35-3.81; P=0.004). In a dose-response meta-analysis of observational studies, dietary lycopene intake was associated with a reduced risk of prostate cancer [relative risk (RR), 0.86; 95% CI, 0.75-0.98], and a 3% reduction in prostate cancer risk was associated with the consumption of a 1 mg/day increment of dietary lycopene intake (95% CI, 0.94-0.99) (100). Ansari and Gupta (101) administered 10 mg/day lycopene to 20 patients with metastatic hormone refractory prostate cancer for 3 months. Only 1/18 patients with associated lower urinary tract symptoms had complete response and 61% experienced improvements of uroflowmetry (Q_{max} ≥12 ml/sec), indicating the effectiveness in the treatment of metastatic hormone refractory prostate cancer. Furthermore, the patients experienced improvements in bone pain and lower urinary tract symptoms. Zhang *et al* (29) assessed the effect of lycopene (10 mg/day) on the prostate-specific antigen (PSA) velocity in a phase II study in Chinese patients with prostate cancer. The average treatment time was 6 months and the average fall in PSA was equivalent to 2.56% over the first 3 months (average slope/day of -0.00028), and in the last 3 months, the average fall in PSA was equivalent to 31.58% (average slope/day of -0.00351; P=0.0009). In another phase II randomized trial of lycopene-rich tomato extract (containing 30 mg/day lycopene) in 58 patients with high-grade prostatic intraepithelial neoplasia (HGPIN), there were no notable differences in the concentrations of PSA, IGF-1 or IGFBP3 between the groups after treatment; however, more extensive atrophy and less extensive HGPIN was more common in the lycopene group than the placebo group (30).

Breast cancer. Breast cancer is the most commonly diagnosed type of cancer and a leading cause of cancer mortality in women (1). In a large prospective analysis of patients with breast cancer with 20 years of follow-up, the association with lycopene was reported to be stronger with measures ≥10 years (the time from blood collection to diagnosis ranged ≥10 years) compared with <10 years before diagnosis [top compared with bottom quintile RR of ≥10 years, 0.69 (95% CI, 0.50-0.94; P=0.01); RR of <10 years, 0.87 (95% CI, 0.70-1.07; P-=0.14); P-heterogeneity=0.09] (15). IGF-1 is an important growth factor associated with an increased risk of premenopausal breast cancer (31). A randomized, placebo-controlled, double-blind, crossover trial was employed to evaluate whether lycopene supplementation (30 mg/day) decreased serum levels of total IGF-1 and IGFBP in premenopausal women with a history of breast cancer or a high familial breast cancer risk (31). Results from

the two study populations demonstrated that total IGF-1 and IGFBP3 were increased in the breast cancer survivor population [total IGF-1, 7.0% (95% CI, -0.2-14.3); IGFBP3, 3.3% (95% CI, 0.7-6.0)], and free IGF-1 was decreased in the family history population (-7.6%; 95% CI, -14.6-0.6). This indicated that lycopene supplementation may have beneficial effects in high-risk healthy women but not in breast cancer survivors (31). However, the study suggested that the inconsistency in IFG-1 levels between breast cancer survivors and high-risk women may be due to specific mutations such as BRCA1 or due to chance. We hypothesize that, in addition to the aforementioned reasons, the subtype classification of breast cancer may also be the potential cause for the results, as different estrogen receptor (ER)/progesterone receptor (PR) states are associated with heterogeneity in patients with breast cancer (102). To the best of our knowledge, previous research has not considered this issue. Moreover, it has been reported that the levels of IGF-1 and IGFBP3 are associated with CRC (103). Tomato lycopene extract (containing 30 mg/day lycopene) was reported to decrease the circulating IGF-1 and the IGF-1/IGFBP3 ratio in patients with CRC, which suggested a preventive effect of lycopene (104).

Gastric cancer. Gastric cancer was the fifth frequently diagnosed cancer in 2022 (1). In a case-control study in Korea, a higher intake of dietary lycopene (≥1.88 mg/day) was inversely associated with overall gastric cancer risk (OR, 0.60; 95% CI, 0.42-0.85; P=0.012). Furthermore, this trend was reported in both men (OR, 0.60; 95% CI, 0.39-0.93) and women (OR, 0.54; 95% CI, 0.30-0.96; P=0.039] after subgroup analyses (105). Furthermore, a notable association between dietary lycopene intake and gastric cancer risk was also observed in subgroups of *Helicobacter pylori*-positive subjects and former smokers (105).

A prospective cohort study including 22,835 participants with different cancer types and lycopene intake (0.485-9.365 mg/day) reported that lycopene intake was associated with a low risk of cancer mortality (HR, 0.79; 95% CI, 0.74-0.82), and after adjusting for competing risks, the sub-HR was 0.82 (95% CI, 0.78-0.86; P<0.001) (14). In the Health Professionals Follow-up Study of 3,977 patients diagnosed with colon adenoma, lycopene intake was inversely associated with colon adenoma (top compared with bottom quintile OR, 0.83; 95% CI, 0.74-0.93; P≤0.001) and this association did not vary by smoking status and alcohol consumption (106). In a follow-up study performed in a rural area of Japan with 3,182 patients, a high level of serum lycopene was reported to reduce the risk of mortality from lung, colorectal and stomach cancer (P=0.01). These findings indicate that lycopene may be a promising biomarker to predict mortality from colorectal and stomach cancer in rural inhabitants in Japan (107). Furthermore, Huang *et al* (108) developed a meta-analysis to assess the association between vitamin A, retinol and carotenoids intake and pancreatic cancer risk. The results demonstrated that a high level of vitamin A, carotene, β-carotene and lycopene intake were associated with a low risk of pancreatic cancer (for lycopene, pooled OR, 0.84; 95% CI, 0.73-0.97; P=0.02).

As lycopene can enhance the sensitivity of anticancer drugs, researchers have also performed clinical studies on drug combination therapy. Zhuang *et al* (16) performed a phase II study to assess the activity of docetaxel (75 mg/m^2) plus lycopene (30 mg) in 13 patients with advanced castrate resistant adenocarcinoma of the prostate. The primary endpoint was set as ≥50% reduction in PSA and the median time to PSA progression was 8 months (95% CI, 3.5-8.7). Median duration of response was 7.3 months (95% CI, 4.8-13.2) and the median overall survival at 5 years was 35.1 months (95% CI, 25.7-57.7). The PSA response rate was 76.9%, with a median survival of 35.1 months, which demonstrated beneficial effects compared with the 45% PSA response rate and median survival rate of 17.4 months reported by the TAX-327 trail (109). Lilly *et al* (32) performed a phase I trial to identify an optimum dose of synthetic lycopene (30, 90 or 150 mg/day) in combination with docetaxel [75 mg/m^2 and androgen blockade, namely androgen deprivation therapy (ADT)] to evaluate its effect on the safety and pharmacokinetics of docetaxel in 24 participants with metastatic prostate cancer. The maximum tolerated dose was identified as 150 mg/day lycopene in combination with docetaxel/ADT for the treatment of patients with metastatic prostate cancer and the synergistic effect was mechanistically associated with angiogenesis and IGF-1 signaling.

Several clinical studies have been performed with lycopene for the treatment of cancer worldwide; however, the results of have not yet been published. Therefore, relevant studies on registering lycopene for cancer treatment were supplemented using ClinicalTrials.gov (Table III), which demonstrated that current research largely comprises phase I and II trials with a relatively small number of participants. Moreover, certain results of epidemiological and clinical trials were inconsistent in determining the relationship between beneficial effects and lycopene intake (110-113), which may be due to limitations such as regional dietary patterns and lifestyle habits. The bioavailability of lycopene is influenced by dietary patterns, especially when consumed together with fat, which can increase the bioavailability of lycopene. A previous study reported that, after consumption of fat-free salad dressing, the detected lycopene content in plasma chylomicrons could be disregarded; however, as the fat content of salad dressing increased, consumption of full-fat salad dressing led to higher levels of lycopene in the blood compared with the consumption of low-fat salad dressing (114). Similarly, dietary lipid sources such as avocados have been reported to markedly increase the absorption of lycopene in salad dressings (115). In addition, the type and emulsifying properties of dietary fat are key for the absorption of carotenoids (42). Therefore, in clinical research, it is not only necessary to control the intake of dietary fats, but also to control the types of dietary fats consumed to eliminate differences associated with dietary patterns. Furthermore, smoking intensity may be a factor affecting the results. Shareck *et al* (116) reported that high levels of β-carotene, α-carotene, lycopene and cryptoxanthin intakes were associated with a decreased risk of lung cancer in male heavy smokers. Min and Min (117) also reported no association between serum lycopene level and lung cancer death among non-smokers and former smokers. However, current research on stratified analysis of smoking intensity mainly focuses on lung cancer, and no studies have been observed to investigate the association between lycopene and smoking in other types of cancer, and smoking intensity as an important

Table III. Ongoing or completed clinical trials of lycopene for cancer prevention and treatment.

Registered trial code	Conditions	Interventions	Phase	Number of participants
NCT01443026	Intraepithelial prostatic neoplasia; prostatic neoplasms	30 mg lycopene	II	66
NCT00068731	Prostate cancer	Lycopene	II	47
NCT00006078	Prostate cancer	Lycopene	I	Unknown
NCT00093561	Prostate cancer	Lycopene	I	Unknown
NCT01882985	Adenocarcinoma of the prostate; recurrent prostate cancer; stage I prostate cancer	Docetaxel, lycopene	II	14
NCT00322114	Prostate cancer	Lycopene	Unknown	150
NCT00178113	Intraepithelial prostatic neoplasia	Lyc-O-Mato® (contains 30 mg/day lycopene), certagen (multivitamins with minerals)	I	80
NCT01949519	Adenocarcinoma of the prostate	Docetaxel, lycopene	I	24
NCT00416390	Prostate cancer	Lycopene	Unknown	120
NCT00042731	Prostate cancer	Lycopene, multivitamin, soy isoflavones	Unknown	79
NCT00416325	Prostate cancer	Lycopene	I	18
NCT00402285	Prostate cancer	Lycopene, fish oil	Unknown	84
NCT01105338	Prostate cancer	Lycopene capsules, green tea capsules, tomato rich diet	II and III	126
NCT00450749	Adenocarcinoma of the prostate; stage I prostate cancer; stage II prostate cancer	Lycopene, surgery	II	10
NCT00844792	Prostate cancer	Lycopene, vitamin D3, selenium, green tea extract, vitamin E	II	48
NCT00744549	Prostate cancer	Lycopene, vitamin D3, selenium, green tea extract, vitamin E	II	16
NCT00450957	Healthy, no evidence of disease; prostate cancer	Lycopene	I	20
NCT03167268	Colorectal cancer metastatic	Lycopene	II	28

NCT, National Clinical Trial.

factor affecting research results also provides potential theoretical support for the study of other types of cancer. Moreover, in analyses stratified by histological subtype of lung cancer, a high intake of lycopene was associated with a reduced risk of squamous cell lung carcinoma but not adenocarcinoma and small cell lung carcinoma (116).

Previous research has also reported that different ER/PR statuses are an important factor in the response of cancer cells to treatment with lycopene (118), indicating that cancer subtype classification is also a vital factor affecting the results. In addition, different formulations of lycopene (natural or synthetic) may also be notable factors. Aust *et al* (119) assessed the photoprotective effects of lycopene from different sources including synthetic lycopene, tomato extract (Lyc-o-Mato®) and tomato drink (Lyc-o-Guard-Drink) in 36 healthy individuals. Participants who consumed tomato extract and tomato drink demonstrated a 38 and 48% reduction in sunburn at week 12, respectively, whereas the group treated with synthetic lycopene had a 25% reduction. This may have been caused by a difference in efficacy between tomato products and synthetic lycopene possibly due to the presence of phytofluene and phytoene, which are the precursors of lycopene (119). A similar study suggested that ethnicity may also be a factor affecting the efficacy of lycopene (99); therefore, multicenter, randomized, double-blind and long term high-quality clinical studies are warranted to verify the efficacy of lycopene.

6. Variation in genes drive precise lycopene therapy

As previously mentioned, SNP variations can affect the bioavailability of lycopene. Therefore, in-depth research on the impact of genetic variations on lycopene plasma/tissue responses may contribute to further understanding of the relationship between natural compounds and health, and guide personalized lycopene therapy. In a meta-analysis of a multiethnic population (African-, Hispanic- and European-American) of postmenopausal women, the scavenger receptor class B, member 1 (SCARB1) gene, which encodes

a cholesterol membrane transporter, was markedly associated with serum lycopene level (rs1672879) (120). Furthermore, the slit homolog 3 gene (rs78219687) and the dehydrogenase/reductase member 2 gene (DHRS2; rs74036811) were markedly associated with lycopene concentrations in African-American individuals in the unadjusted model. After adjustment for total cholesterol only, the variants in the DHRS2 region remained notable (120).

Watermelon is a rich source of lycopene and Crowe-White *et al* (121) performed a randomized controlled crossover study with postmenopausal women which reported that serum lycopene not only exhibited notable therapeutic effect, but also demonstrated marked inter-individual responses, and these were associated with the BCO1 (rs6564851) variant. Moreover, in patients with prostate cancer, different intake levels of tomato-soy juice were reported to affect the BCO1 single nucleotide polymorphism (SNP; rs12934922 and rs6564851) effects in magnitude and direction, but no notable trend of SCARB1 (rs11057841) genotype effect for the prediction of plasma phytofluene level was observed (122). Additionally, in a study with healthy male participants, 28 SNPs in 16 genes were reported to be associated with 72% of the variance in the postprandial plasma chylomicrons lycopene response (123). In addition, the variant of SETD7 (rs7680948) was markedly associated with serum lycopene concentrations in 441 adults. Meanwhile, an association of lycopene levels with a different SNP (rs11057841) in SCARB1 was observed, which provided nominal evidence for previous studies (124). Therefore, the aforementioned results support that genetic variation is an important factor in reflecting differences in lycopene levels between individuals; however, as the studies were performed using single sex populations, sex differences in the association between the genetic variant and serum lycopene concentrations could not be evaluated.

Furthermore, different cancer subtypes defined by certain characteristics (such as menopausal status or expression of genes and proteins status) may have different risk characteristics, which are important factors affecting research results. For example, the ER and PR status is usually used to define the subtype of breast cancer (102). Cui *et al* (125) studied the association between carotenoids and the risk of hormone receptor-defined invasive types of breast cancer in postmenopausal women. The study reported a lower risk of ER^+/PR^+ breast cancer associated with α-carotene, β-carotene and lycopene intakes, when comparing the highest with the lowest quintiles of intake; however, no associations were observed for other breast cancer groups jointly defined by their ER and PR status. Moreover, a meta-analysis demonstrated that lycopene was inversely associated with breast cancer and exhibited stronger associations for ER^- compared with that for ER^+ tumors (126). Stratified analyses by menopausal status and ER/PR status also revealed that serum α-carotene, β-carotene, lycopene and lutein/zeaxanthin were inversely associated with breast cancer risk among Chinese premenopausal women and among all subtypes of ER or PR status (127). An *in vitro* study has also reported that ER status is an important factor in the response of cancer cells to treatment with carotenoids and retinoids (118).

Therefore, studies that analyze cancer as a single factor may dilute or even mask the effects that may be caused by cancer subtypes. Further research is warranted to explore the relevant genetic variation factors to clarify the exact role of lycopene in cancer. Additionally, the association between the aforementioned genes and lycopene requires large-scale population studies. The ultimate aim of these studies should be to provide an accurate genetic tool to predict individual lycopene bioavailability, obtain the optimal dosage for individuals and regulate disease risk by adjusting the intake of lycopene.

7. Conclusions and perspectives

Cancer is a major cause of death worldwide and the development of novel anticancer drugs is an effective means to alleviate this. Lycopene, an easily obtained natural compound abundant in nature, has several health benefits as well as high application prospects and commercial value. Epidemiological data has demonstrated that lycopene is associated with a reduced risk of certain cancer types and with the combination of therapeutic drugs, it may enhance efficacy and antitumor activity. Moreover, novel delivery systems may markedly improve its bioavailability. Lycopene may prove to be an effective strategy for future cancer prevention and treatment; therefore, further study is worthwhile.

Although there is currently a large amount of research evaluating the anticancer effects of lycopene, it is still insufficient to assess its full potential in the field of cancer. Due to instability caused by temperature and other factors, there may be contradictions between *in vitro* and *in vivo* research results. In addition, due to differences in dietary patterns and lifestyle habits, further research is necessary to explore effective doses of lycopene and clarify the relationship between beneficial effects and intake. Therefore, translational pharmacology studies are warranted to validate the anticancer activity of lycopene. Furthermore, high-quality clinical trials, such as multi-center, double-blinded, randomized controlled studies are required to assess the effects of lycopene and the synergistic effects with other chemotherapy drugs (e.g. docetaxel, 5-FU, cisplatin). Dietary intake can also affect the bioavailability of lycopene, and the development of novel delivery systems, such as natural carrier of extracellular vesicles, has markedly improved the bioavailability of lycopene. In addition, it is necessary to strengthen the research of lycopene-related SNPs to achieve precision medicine. Perhaps with the precise use of lycopene and with the collaborative application of multiple omics such as genomics, transcriptomics, artificial intelligence and big data, pathway-specific dependencies of lycopene can be elucidated.

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Authors' contributions

JR conceived and designed the review topic. SY wrote the manuscript. XX and YL prepared the figures. XX, YL, HF and JR revised the manuscript. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

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Competing interests

The authors declare that they have no competing interests.

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