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# Antioxidant, anticancer activity and molecular docking study of lycopene with different ratios of Z-isomers

Haiyan Wang [a,1], Yanting Lin [a,1], Qingsong Liu [a], An Zhou [b], Huixi Bian [a], Wencheng Zhang [a], Ailing Hui [a], Zeyu Wu [a,*]

[a] Engineering Research Center of Bio-Process of Ministry of Education, School of Food and Biological Engineering, Hefei University of Technology, Hefei, 230601, China
[b] The Experimental Research Center, Anhui University of Chinese Medicine, Hefei, 230038, China

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ABSTRACT

The main purpose of this study was to compare the antioxidant and anticancer activities of lycopene samples with different ratios of Z-isomers. Lycopene samples containing 5%, 30%, and 55% Z-isomers were successfully prepared by using thermal treatment combined with anti-solvent crystallization. The *in vitro* bio-accessibility of lycopene was estimated by the determination of partition factor (PF) and the results showed that lycopene with 55% Z-isomers possessed the highest bio-accessibility. Moreover, DPPH and ABTS assays suggested that the antioxidant activity of lycopene increased with the Z-isomers content from 5% to 55%. However, lycopene inhibited the survival of human hepatocellular carcinoma cells (HepG2) in a dose and time-dependent manner. The highest inhibition of HepG2 cell lines was achieved by 55% Z-ratio of lycopene. The cell viability was 22.54% at 20 μg/mL after incubating for 24 h, the number of cells was significantly reduced and the morphology was shrunk. Furthermore, molecular docking was introduced to compare the binding ability between different lycopene isomers with Scavenger Receptor class B type I (SR-BI), and the results revealed that the affinity of (all-E)-lycopene with SR-BI was lower compared to 5Z-lycopene and 13Z-lycopene, providing the reasons for different bioavailability of the above-mentioned lycopene isomers. All the above results demonstrated that Z-isomers-rich lycopene could enhance bio-accessibility and biological functionality.

## 1. Introduction

Lycopene is extensively found in various kinds of fresh fruits and vegetables, such as tomatoes, watermelons, guavas, and grapefruits (Srivastava and Srivastava, 2015; Hernández-Almanza et al., 2016). Chemically, lycopene is a symmetrical acyclic carotenoid with 13 double bonds, 11 of which are conjugated, thus it is susceptible to being geometrically isomerized (Takehara et al., 2014). Based on the relative potential energies of (all-E)- and mono-Z-isomers of lycopene (all-E ≈ 5Z > 9Z > 13Z) and the magnitudes of activation energy of (all-E)-lycopene isomerized to each mono-Z-isomer (5Z > 9Z > 13Z-lycopene), (all-E)- and (5Z)-lycopene are more stable compared to 9Z- and 13Z-isomers (Chasse et al., 2001; Guo et al., 2008). Although (all-E)-lycopene is the most predominant geometric isomer existing in plants (Kong et al., 2010), Z-isomers account for more than 50% of total lycopene in human serum and different tissues (Richelle et al., 2010, 2012; Clinton et al., 1996). Similar trends have also been observed after food processing and storage. Furthermore, the relatively higher bio-availability of lycopene Z-isomers has been confirmed (Failla et al., 2008; Böhm et al., 2002; Honest et al., 2011). For example, the results of quinone reductase, nitric oxide inhibition bioassays as well as *in vivo* and *in vitro* lymphatic ferrets experiments revealed that the bio-availability of Z-isomers was higher than that of all-E-form (Zhang et al., 2012; Boileau et al., 1999). Besides, thermal treatment and dehydration could induce the E/Z isomerization of lycopene, particularly in oil or different organic solvents (Colle et al., 2010; Honda et al., 2015a, 2017a). Therefore, the interest in the isomerization of (all-E)-lycopene to Z-isomers has received increased attention.

The bio-activity of natural compounds is closely related to their chemical structures. That is to say, for lycopene, the isomerization of (all-E)-lycopene to the Z-isomers would cause activity changes. According to previous studies, lycopene possesses different kinds of biological properties, including antioxidant activity, anti-inflammatory and reducing the incidence of cancer, cardiovascular and coronary heart

* Corresponding author.
*E-mail address:* wuzeyu@hfut.edu.cn (Z. Wu).
[1] These authors contributed equally to this paper.

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diseases (Choi et al., 2014; Soares et al., 2019). Previous studies mainly focused on the identification and structural differences between E/Z formations, the antioxidant and anticancer activities of (all-E)-lycopene, and so on. However, the comparison of lycopene with different ratios of Z-isomers is rarely reported. Therefore, it is desirable to explore the relationship between the ratio of Z-isomers and the bio-activities of lycopene, including antioxidant and anticancer activities. Meanwhile, whether the antioxidant activity is conducive to the anticancer activity of lycopene isomers still needs to be investigated.

Except for chemical structure, digestibility is also regarded as an important factor affecting the bioactivity of compounds. The improvement of absorption performance of lycopene isomers will be beneficial to their actions on human health. It is well known that the transport process of bioactive compounds in the body always seriously affects bioavailability, i.e., the combination of bioactive compounds with different transporters is an important factor. Moreover, recently published references reported that scavenger receptor class B type I (SR-BI), an enterocyte apical membrane transporter, played an important role in the adsorption process of carotenoids (During et al., 2005; Yang et al., 2019). To the best of our knowledge, the transport mechanism and the relationship between the transport process and the bio-activity of lycopene isomers, have not been fully explored. Meanwhile, the molecular docking experiment is regarded as a good choice to find out why the bioactivity of lycopene is extremely affected by different kinds of isomers.

Therefore, the purpose of this study was to investigate the antioxidant and anticancer activities of lycopene with different ratios of Z-isomers. The lycopene with different proportions of Z-isomers was prepared by thermally-induced geometrical isomerization and anti-solvent crystallization, and then the bio-accessibility, anti-oxidative effect, and anticancer activity of different proportions of Z-isomers were compared. The experimental results are expected to provide useful information related to the potential activities of Z-isomers of lycopene.

## 2. Materials and methods

### 2.1. Materials and reagents

Tomatoes were bought from a local supermarket (Anhui, China). (All-E)-lycopene and β-carotene standards (purity ≥98%) were purchased from Sangon Biotech Co., Ltd (Shanghai, China). Chromatographic grade acetonitrile and tetrahydrofuran were obtained from Shanghai Yihe Biological Technology Co., Ltd (Shanghai, China). Human hepatocellular carcinoma (HepG2) cells and human umbilical vein endothelial cells (HUVECs) were purchased from ATCC (Manassas, VA, USA). Cell culture medium and supplements were supplied by HyClone (Logan, UT, USA). All other reagents were supplied by Sinopharm Chemical Reagent Co., Ltd (Shanghai, China).

### 2.2. Thermal isomerization of (all-E)-lycopene

The preparation process of lycopene samples with different proportions of Z-isomers is illustrated in Fig. S1. Firstly, 100 g of tomato was washed with distilled water, cut into small pieces, juiced, and dissolved in 80 mL $CH_2Cl_2$. After ultrasonic-assisted homogenization for 15 min and centrifugation at 4000 rpm for 10 min, the residue was repeatedly extracted with $CH_2Cl_2$ until the filtrate became colorless. The collected solution was combined, concentrated to a concentration of 0.1 mg/mL, and heated under reflux in an oil bath at 50 °C for 12 h (Murakami et al., 2018). The headspace of the condensate tube was filled with $N_2$ and tightly capped to prevent oxygen from entering the tube. After the reaction, samples were divided equally into two parts, in which one named as No. 2 was stored at −20 °C, while the other was used for further experiments. After $CH_2Cl_2$ was removed by an evaporator, the residue was re-dissolved in 5 mL acetone at 40 °C. Then, the acetone solution was re-crystallized by using reverse solvent cryogenic crystallization at 4 °C. The obtained crystals (No. 1) and the filtrate (No. 3) were collected. Finally, three different samples, i.e., No. 1, No. 2, and No. 3, were blow-dried under $N_2$ and the lycopene isomer was analyzed by using high performance liquid chromatography (HPLC).

### 2.3. Determination of lycopene

For UV analysis, the full-wavelength scanning was performed by using a UV-2600 ultraviolet spectrophotometer (MPT Instruments Co., Ltd, Shanghai, China) within 200–600 nm. HPLC analysis was carried out using an Agilent 1260 chromatographic system (Agilent Technologies, Santa Clara, USA). The separation was achieved on a cosmosil cholester column (4.6 mm × 250 mm, 5 μm, Nacalai Tesque, Kyoto, Japan) with a mobile phase containing acetonitrile and tetrahydrofuran (83:17, v/v) at 25 °C. After 20 μL of samples were injected at 1.0 mL/min, the quantification of E/Z isomers was performed by peak area integration at 472 nm.

### 2.4. Bio-accessibility of lycopene

According to the absorption and transport process of carotenoids, lycopene needs to be dissolved into oil before being transferred to the mixed micelles in the small intestine (Palmero et al., 2014). Based on the previous study with some modifications (Sun et al., 2016), the *in vitro* bio-accessibility of lycopene was estimated by the determination of partition factor (PF). Briefly, 5%, 30%, and 55% total Z-ratio of lycopene samples were prepared in acetone (200 μg/mL), respectively. The lycopene samples (1 mL) were mixed with 0.1 mL of bile salt solution in a 15 mL centrifugation tube and then dried with blowing nitrogen. After that, 5 mL of deionized water and 5 mL of olive oil were added to all tubes and flushed with nitrogen in the headspace of the samples. All reactions were terminated after 5, 10, 15, 20, 25, and 30 min at 37 °C. Finally, 0.2 mL of the upper oil phase was diluted with acetone to 5 mL after centrifugation at 4000 rpm for 5 min, and then the lycopene content was determined by using a UV–Vis spectrophotometer at 472 nm.

$$PF = M_{oil}/M_i$$

Where $M_{oil}$ and $M_i$ were the content of lycopene diffused into oil and initial lycopene content, respectively.

### 2.5. In vitro antioxidant activity

#### 2.5.1. DPPH radical scavenging activity

DPPH radical scavenging activity of lycopene samples was determined based on the method of (Kelebek et al., 2017) with some modifications. Briefly, the mother liquor of lycopene (1 mg/mL) was prepared and serially diluted to 1–400 μg/mL with acetone. Then 3 mL of DPPH ethanol solution ($6 \times 10^{-5}$ M) was added to 0.1 mL of different diluents, fully shaken, and then kept in darkness at 25 °C for 30 min. The absorbance was immediately recorded at 517 nm.

#### 2.5.2. $ABTS^+$ radical scavenging activity

ABTS radical scavenging activity of lycopene samples was evaluated according to the method of (Bamidele and Fasogbon, 2017). Equal volumes of ABTS (7.4 mM in water) and potassium persulfate (2.6 mM in water) were mixed and stood in darkness for 12 h to generate ABTS radicals. Before the assay, the ABTS solution was diluted with ethanol to an absorbance of 0.70 ± 0.02 at 734 nm. Then, 0.1 mL sample solution was added to 3 mL of diluted ABTS solution with sufficient mixing in darkness at 25 °C for 30 min, and the absorbance was read at 734 nm.

### 2.6. CCK-8 assay for growth inhibition of cells

The cell viability was determined using the Cell Counting Kit-8 (CCK-8) colorimetric assay. Cells were routinely maintained in Dulbecco's

Modified Eagle's Medium (DMEM) supplemented with 100 U/mL penicillin, 100 mg/mL streptomycin, and 10% fetal bovine serum (FBS, ExCell Bio, Shanghai, China) in a humidified 5% $CO_2$ incubator at 37 °C. The lycopene samples were completely dissolved in DMSO to 1 mg/mL, and then serially diluted with the culture medium to 1, 5, 10, 20, and 50 μg/mL. HepG2 cells and HUVECs were seeded into a 96-well plate (100 μL) at a density of $5 \times 10^3$ cells/well in a 5% $CO_2$ incubator at 37 °C for 24 h. Subsequently, the medium was decanted and added with 100 μL of lycopene samples in different concentrations. Meanwhile, for the control group, only 100 μL of culture medium was added. The cells were incubated in a humidified atmosphere of 5% $CO_2$ at 37 °C for 24 h and 48 h, and the morphology of HepG2 cells treated with lycopene samples for 24 h was observed by using a microscope (IX71, Olympus, Japan). After 10 μL of CCK-8 solution was added and continued to culture for 1 h, the absorbance of each well was measured by using an ELX800 microplate reader (BioTek Instrument, Highland Park, USA) at 450 nm.

### 2.7. Molecular docking experiment

The molecular docking experiment was carried out based on the previous reference with some modifications (Yang et al., 2019). Firstly, from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/), 3D structures of different lycopene isomers, including (all-E)-lycopene (PubChem CID: 131954643), 5Z-lycopene (PubChem CID: 11756979), and 13Z-lycopene (PubChem CID: 6440310) were obtained. After that, the 3D structural model of *Homo sapiens* Scavenger Receptor class B type I (SR-BI, NCBI accession# NP_001076428.1) was built by using the online software of SWISS-MODEL (https://swissmodel.expasy.org/interactive/). Finally, Discovery Studio (version 4.5, BIOVIA, USA) was used to accomplish the docking of the above lycopene isomers with the SR-BI transporter.

### 2.8. Statistical analysis

The experiments were repeated in triplicate and the results were expressed as mean ± standard deviation (SD). Statistical analysis of the variance (factorial ANOVA) with a confidence level of 95% ($P < 0.05$) was performed using SPSS 17.0 software (SPSS Inc., Chicago, IL, USA).

## 3. Results and discussion

### 3.1. Isomerization analysis

HPLC chromatogram of isomerized and crystallized lycopene samples, as well as purified (all-E)-lycopene is illustrated in Fig. 1. Compared to the previous study (Zhang et al., 2012), the separation method of lycopene E/Z isomers was further improved. To be specific, not only the separation effect of E/Z isomers was nearly equal to that of using three connected Nucleosil 300–5 columns, but also the experimental operation was relatively simple with shortened separation time. Lycopene samples (all-E isomer >90.0%) were successfully purified from tomatoes. After 12 h of refluxing, the total Z-ratio of isomers showed an increase from an initial 10%–30% (Sample NO. 2, Fig. 1B). Then, the filtrate (Sample NO. 3, Fig. 1C) and residue (Sample NO. 1, Fig. 1A) obtained by crystallization separation were composed of 55% and 5% Z-isomers, respectively.

(All-E)-lycopene and β-carotene were confirmed by using the relevant standards. Meanwhile, the Z-isomers of lycopene were identified according to retention time in HPLC, visible spectral data, and the relative intensity of Z-peak (% $D_B/D_{II}$), as previously reported (Zhang et al., 2012; Murakami et al., 2018; Honda et al., 2015b; Frohlich et al., 2007; Schierle et al., 1997). From Table S1, the (all-E)-lycopene content was the highest (44.5%), followed by (13Z)-lycopene (up to 21.2%), accounting for 38.6% of Z-configurations. Additionally, the intensity of (13Z)-peak ($D_B/D_{II}$) was the highest, up to 55%, which was consistent with the statement that the closer the Z-part of the conjugated chain of

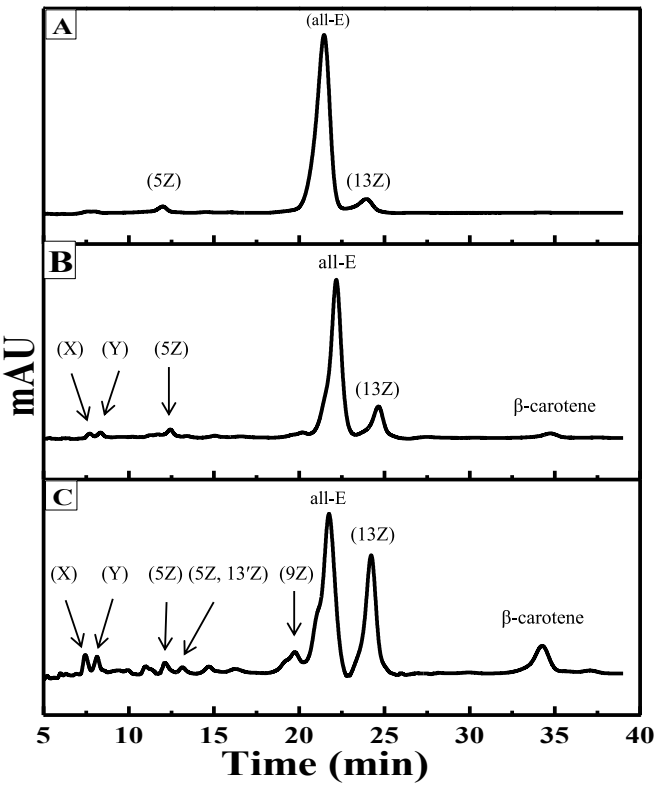


**Fig. 1.** HPLC chromatograms of lycopene. (A) 5% total Z-ratio of lycopene, (B) 30% total Z-ratio of lycopene and (C) 55% total Z-ratio of lycopene, and X, Y = unidentified samples.

lycopene was to the center, the higher the Z-characteristic peak (Stahl et al., 1993). It was reported that (all-E)- and (5Z)-lycopene were more stable compared to (9Z)- and (13Z)-isomers. Interestingly, (5Z)-lycopene showed higher bioavailability and antioxidant capacity than (all-E)-lycopene, (9Z)- and (13Z)-lycopene (Richelle et al., 2012; Müller et al., 2011). In this study, the result that (5Z)-isomer with a relatively low intensity was similar to the previous study, thus it was significant to obtain lycopene products rich in Z-isomers, especially (5Z)-lycopene (Honda et al., 2015a; Murakami et al., 2018).

### 3.2. UV–Vis spectra analysis

The Z-isomers of lycopene can be identified by UV–Vis spectrometry due to the blue shift of the maximum absorption wavelength and the presence of the "Z" peak at around 360 nm (Saleh and Tan, 1991; Phan-Thi and Waché, 2014). In Fig. 2A, compared with the 5% total Z-ratio of lycopene, the blue shift of the maximum absorption wavelength of 30% total Z-ratio of lycopene was not obvious at 474 nm, but a strong absorption peak appeared at 363 nm. In addition, for 55% total Z-ratio of lycopene, both a blue shift of 6 nm and a strong absorption peak at 363 nm were observed. These experimental results suggested that with the Z-configuration ratio of lycopene increasing, the blue shift of the maximum absorption peak and the absorption peak at 363 nm were more obvious, which could be explained by the fact that the large electron delocalization range and small bond tension of (all-E)-lycopene caused the $\pi \rightarrow \pi^*$ transition located at the long-wave end. Besides, the steric hindrance of Z-isomer weakened the conjugation effect, leading to the absorption peak shift to the short wavelength (Honda et al., 2017b).

### 3.3. Bio-accessibility evaluation

The effect of the relative proportion of Z-isomers on the bio-accessibility of lycopene is illustrated in Fig. 2B. As expected, after 30

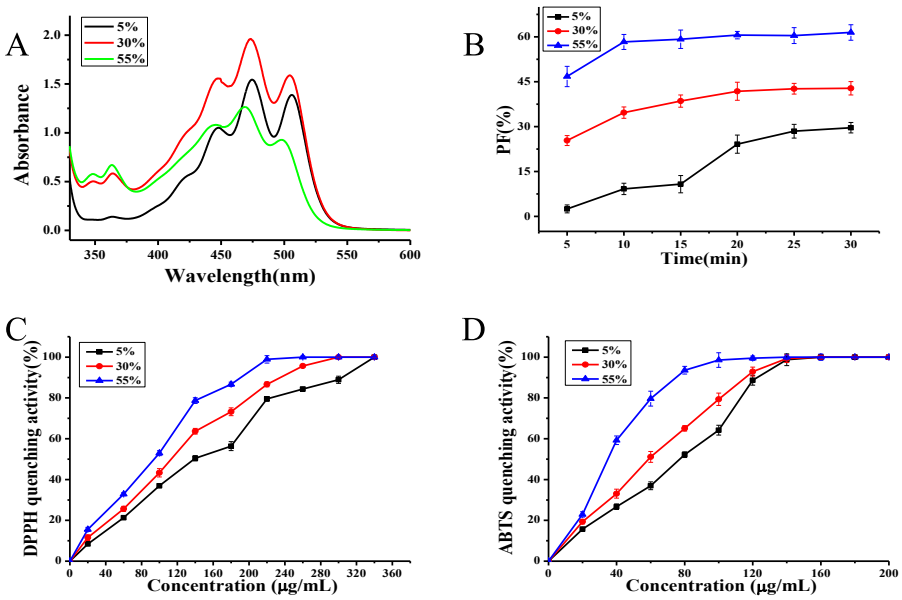


**Fig. 2.** The properties of lycopene with different ratios of Z-isomers. (A) UV–Vis spectra of lycopene, B) Bio-accessibility of lycopene, (C) DPPH quenching activities of lycopene and (D) ABTS quenching activities of lycopene.

min of gentle mixing, the PF value distinctly increased from 29.64% to 61.48% with the total Z-ratio of lycopene from 5% to 55%, that is to say, more than twice increase in PF value. Moreover, 55% of total Z-ratio of lycopene reached the maximum PF value only within 10 min, while 30% and 5% total Z-ratio of lycopene reached the maximum PF value after 25 min. These results indicated that Z-isomers of lycopene are more easily soluble in olive oil than all-E-isomer, which was in accordance with the results described by (Honda et al., 2017b). The (Z)-isomer curved molecular conformation increases the randomness of the molecule compared to the (all-E)-linear structure, which may be prone to micronization and emulsion in the lipid droplets, thereby preferentially incorporated into chylomicrons and efficiently absorbed by the small intestine (Page et al., 2012; Salvia-Trujillo and McClements, 2016; Mutsokoti et al., 2017; Cooperstone et al., 2015). Moreover, it was reported that the bio-accessibility of lycopene was also related to its physicochemical properties, such as melting point, solubility, and crystallinity (Honda et al., 2015b).

### 3.4. Antioxidant activity analysis

The results of the DPPH scavenging capacity of different lycopene samples are illustrated in Fig. 2C. In general, as the concentration of lycopene samples rose, the DPPH quenching activity increased. Noticeably, 55% of total Z-ratio of lycopene showed the lowest $IC_{50}$ value ($IC_{50}$ = 80 μg/mL) for the inhibitory rates of DPPH radical, followed by 30% ($IC_{50}$ = 110 μg/mL) and 5% ($IC_{50}$ = 140 μg/mL) total Z-isomers. As shown in Figs. 2D and 55% total Z-ratio of lycopene quenched 100.0% of free ABTS radicals starting from lycopene concentration equal to 100 μg/mL, while, at a minimum 140 μg/mL, 30% and 5% total Z-ratio of lycopene, was required to quench 100.0% of free ABTS radicals. The $IC_{50}$ values of 5%, 30%, and 55% total Z-ratio of lycopene for the inhibitory rates of ABTS free radical were about 80, 60, and 35 μg/mL, respectively. The above experimental results proved that lycopene containing a higher ratio of Z-isomers could reveal a higher antioxidant capacity than that of (all-E)-lycopene, which was similar to the report of (Müller et al., 2011). Due to the special conjugated structure, lycopene exhibited strong antioxidant activity, which may be a potential factor connecting with the anticancer effect.

### 3.5. Cell assay

#### 3.5.1. Effect of lycopene on the cell viability of HUVECs

The effects of lycopene containing 5%, 30%, and 55% Z-isomers on the cell viability of HUVECs at different concentrations within 24 h are shown in Fig. 3A. For a low concentration of 1 μg/mL, the effect was not obvious. With the concentration ranging from 5 to 10 μg/mL, the relative cell viability increased significantly, up to about 160.0%, indicating that lycopene had a positive effect on the cell viability of HUVECs. But when the concentration of lycopene increased to 20 μg/mL, the cell growth was inhibited. Moreover, there was no obvious difference in the effect of lycopene containing 5%, 30%, and 55% Z-isomers on normal cells. In conclusion, lycopene did not reveal a killing effect on normal cells within a certain range, which was conducive to further development and application.

#### 3.5.2. Effect of lycopene on HepG2 cell viability

The results shown in Fig. 3B and C suggested that a significant decrease in relative HepG2 cell viability was closely related to the culture time. Specifically, the inhibition ratio of 5% Z-lycopene on liver cancer cells reached 36.0% and 54.0% at 10 μg/mL after cultured 24 h and 48 h, indicating that a time-dependent inhibitory effect on the cell viability was found. Moreover, the cell viability declined to less than 20.0% after administration of 20 μg/mL samples for 48 h. Thus, with the prolongation of time, the inhibition effect of lycopene samples on liver cancer cells was more significant. Taking Fig. 3B as an example, the inhibitory effects of lycopene containing 5%, 30%, and 55% Z-isomers on HepG2 cells were compared as follows. Firstly, the cell viability decreased with the increase of lycopene concentration. Secondly, after 24 h of 5%, 30%, and 55% Z-lycopene administration at a concentration of 10 μg/mL, the cell survival rates were 64.2%, 59.2%, and 39.6%, respectively, which suggested that 55% Z-lycopene had a greater impact on HepG2 cells. Thus, lycopene enriched with Z-isomers could reduce cell viability.

To intuitively observe the inhibitory effect of lycopene on cancer cells, the changes in cell number and morphology were investigated under the microscope after treatment with lycopene samples at a concentration of 20 μg/mL for 24 h (Fig. 4). From Fig. 4A, a large number and normal morphology of HepG2 cells in the control group were observed, while the number of cells in the experimental groups

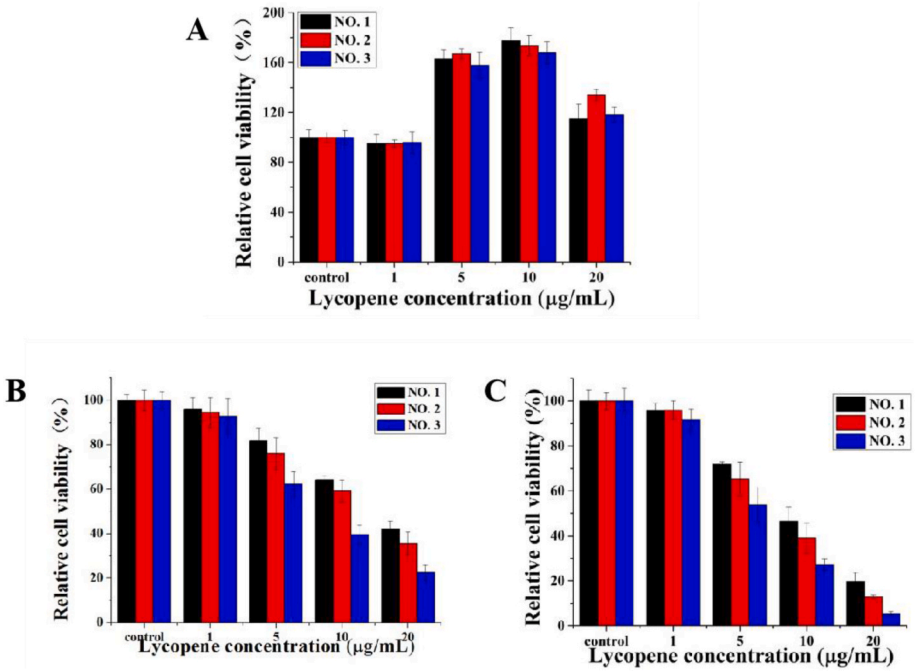


**Fig. 3.** (A) Inhibitory effects of lycopene against HUVEC cells, (B) Inhibitory effects of lycopene against HepG2 cells after incubation for 24 h and (C) Inhibitory effects of lycopene against HepG2 cells after incubation for 48 h.

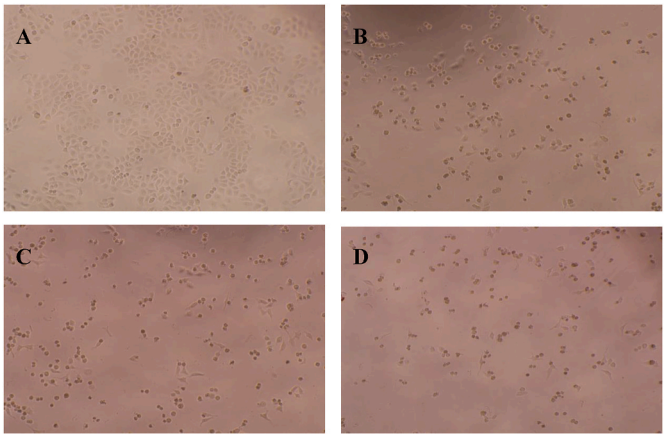


**Fig. 4.** Microscopy of HepG2 cells with different ratio Z-isomers of lycopene at 20 μg/mL. (A) Control group, (B) 5% total Z-ratio of lycopene, (C) 30% total Z-ratio of lycopene and (D) 55% total Z-ratio of lycopene.

gradually decreased with the increase of the Z-configuration content from 5% to 55% (Fig. 4B, C and 4D). To be specific, the least number of live cells were found in the 55% Z-lycopene group (Fig. 4D), followed by 30% and 5% Z-lycopene groups. Moreover, after treated with three different samples, HepG2 cells were obviously shrunk, and the degree of shrinkage was serious with the increase of the Z-configuration content. All the above results revealed that lycopene possessed an obvious inhibitory effect on liver cancer cells, and Z-isomer possessed higher anticancer activity than that of (all-E)-isomer.

### 3.6. Molecular docking

Due to unavailability of the 3D structure of 9Z-lycopene, we only obtained the calculation results of (all-E)-Lycopene and the other two Z-isomers. As the molecular docking results illustrated in Fig. 5, except for (all-E)-Lycopene, the other two Z-isomers were bound within the same proximity of the predicated active transporter pocket. The amino acids that stabilize the interactions between the above isomers with SR-BI might explain the observed changes in substrate binding. For example, amino acids, including PHE201, LEU211, PHE336, and ALA338, are responsible for the binding of 5Z-lycopene with SR-BI (Fig. S2A). And the 13Z-lycopene is stabilized by the following residues: PRO200, PHE201, PHE 208, LEU211, ARG335, ALA338, LEU388, LEU390, and PHE416 (Fig. S2B). However, (all-E)-Lycopene interacts with the SR-BI interface through the following amino acids, PHE199, PRO200, PHE208, ALA279, MET283, LEU370, LEU388, and LEU390 (Fig. S2C). According to the above analysis, no amino acids that existed in binding and transporting all three lycopene isomers have been found.

Besides, the predicted CDOCKER energy, CDOCKER interaction energy, and binding energy of the bindings between lycopene isomers and SR-BI transporter are listed in Table S2. The calculated CDOCKER energy value for (all-E)-lycopene was significantly lower (−111.46) than those values for 5Z-Lycopene (−88.48) or 13Z-Lycopene (−79.64). For CDOCKER interaction energy, the order was (all-E)-lycopene (28.98) < 13Z-Lycopene (46.14) < 5Z-Lycopene (50.23). As is well known, greater CDOCKER energy and CDOCKER interaction energy value imply greater favorable binding between the protein and the ligands. In addition, the binding energy value is positively related to the stability of the binding system. Thus, it could be concluded that (all-E)-lycopene possessed a poor affinity to SR-BI compared to the other Z-isomers.

## 4. Conclusions

In the present study, lycopene samples containing 5%, 30%, and 55% Z-isomers were successfully prepared by using the thermal treatment and anti-solvent crystallization. The solubility of lycopene was found to be an important factor for enhanced bio-accessibility. In addition, compared to 5% and 30% Z-lycopene, 55% total Z-ratio of lycopene revealed the strongest scavenging activity on radical DPPH and ABTS. Moreover, lycopene samples had a positive effect on the cell viability of HUVECs at the concentrations of 5, 10 and 20 μg/mL. But they inhibited the survival and injury of HepG2 cells in a concentration and time-dependent manner. Furthermore, molecular docking results revealed that the affinity of (all-E)-lycopene with SR-BI was lower than 5Z-Lycopene or 13Z-Lycopene. This study could provide an important basis for

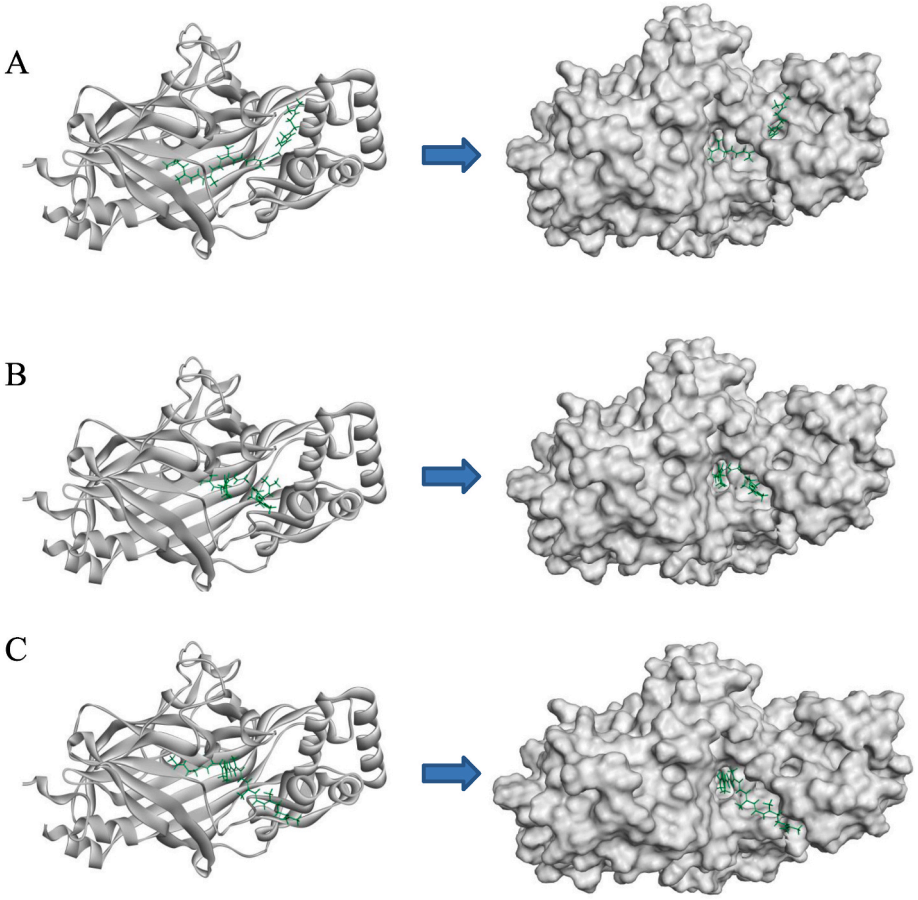


**Fig. 5.** Molecular docking of three lycopene isomers into the binding sites of SR-BI: (A) 5Z-lycopene, (B) 13Z-lycopene and (C) (all-E)-Lycopene.

the study of the differences in the inhibition mechanism of E/Z isomers on cancer cells.

## CRediT authorship contribution statement

**Haiyan Wang:** Investigation, Methodology, Formal analysis, Writing – original draft. **Yanting Lin:** Investigation, Methodology, Writing – original draft. **Qingsong Liu:** Investigation, Methodology. **An Zhou:** Validation, Resources. **Huixi Bian:** Validation, Resources. **Wencheng Zhang:** Conceptualization, Methodology, Resources. **Ailing Hui:** Validation, Resources. **Zeyu Wu:** Conceptualization, Data curation, Writing – review & editing, Supervision, Funding acquisition.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

No data was used for the research described in the article.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.crfs.2023.100455.

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