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Regular Paper

Small daily doses of orange heirloom ("Moonglow") tomatoes dose-dependently increase plasma and liver lycopene concentrations in rats

Umani S. Walallawita[1,*], Frances M. Wolber[2], Ayelet Ziv-Gal[3], Marlena C. Kruger[4], and Julian A. Heyes[2]

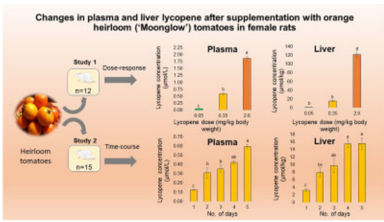
[1]Pro Vice-Chancellors Office, College of Health, Massey University, Palmerston North, New Zealand
[2]School of Food and Advanced Technology, College of Sciences, Massey University, Palmerston North, New Zealand
[3]Department of Comparative Biosciences, College of Veterinary Medicine, University of Illinois at Urbana-Champaign, Urbana, IL, USA
[4]School of Health Sciences, College of Health, Massey University, Palmerston North, New Zealand
*Correspondence: Umani S. Walallawita, u.walallawita@massey.ac.nz

Abstract

Lycopene in red tomatoes is mainly in the poorly bioavailable all-*trans*- isomeric form, while "Moonglow," an orange heirloom tomato, contains more bioavailable *cis*-lycopene isomers. Consuming around 1.5 kg of red tomatoes daily is needed to achieve effective plasma lycopene levels (>0.45 µmol/L). This study hypothesized that small daily doses of "Moonglow" tomatoes could achieve beneficial lycopene levels in rats. Female Sprague-Dawley rats were supplemented with "Moonglow" tomato powder. In Study 1, rats received lycopene at 0, 0.05, 0.35, or 2.6 mg/kg body weight daily for five days. Plasma and liver lycopene concentrations increased dose-dependently. In Study 2, rats given 0.35 mg/kg daily showed dose- and time-dependent increases in lycopene. Plasma lycopene reached 0.42 µmol/L after 4 days, similar to beneficial human levels. These findings suggest that a reasonable daily intake of "Moonglow" tomatoes can achieve effective plasma lycopene concentrations.

Keywords: lycopene, cis- isomers, "Moonglow" tomato, plasma and liver lycopene concentration

Graphical abstract



Changes in plasma and liver lycopene after supplementation with orange heirloom ("Moonglow") tomatoes in female rats.

Lycopene is a lipid-soluble carotenoid produced by plants and some microorganisms (Rao and Ali 2007; Viuda-Martos *et al.* 2014). The molecule exists in all-*trans*- and a variety of *cis*-configurations in nature (Richelle *et al.* 2012). However, *cis*-lycopene isomers have been reported to be more bioavailable than all-*trans*-lycopene (Srivastava and Srivastava 2015). Lycopene in raw red tomatoes predominantly exists in all-*trans*- configurations. Further, lycopene in red tomatoes exists in large crystalline aggregates showing poor solubility in micelles during absorption (Cooperstone *et al.* 2015). Compared to all-*trans*-, *cis*-lycopene is dissolved in lipid droplets, rather than in crystalline form, and is thus highly bioavailable (Ishida *et al.* 2007; Unlu *et al.* 2007). *Cis*- isomers of lycopene possess smaller chain lengths and an overall chemical structure that facilitates its solubility. *Cis*- isomers of lycopene are estimated to be 8.5 times more bioavailable than all-*trans*-lycopene (Unlu 2007; Cooperstone 2015).

Many dietary intervention studies in humans have used daily doses up to 25-30 mg of lycopene as a physiologically relevant dose for the reduction of certain noncommunicable disorders (Bowen *et al.* 2002; Grainger *et al.* 2008; Mackinnon *et al.* 2011; Ried and Fakler 2011). Based on the reported levels of lycopene in red tomatoes and the percentage absorption in the body, a daily dose of 25 mg lycopene would equate to an adult eating 1.5 kg of fresh red tomatoes or 600 gm of tomato sauce (ketchup) daily (Shi and Maguer 2000; Rao and Shen 2002; Rao and Rao 2007; Story *et al.* 2010), neither of which would be easily achievable. This requirement is largely due to the poor absorption of lycopene in the body (Anese *et al.* 2013).

Recent research highlights that *cis*-lycopene not only exhibits higher bioavailability but may also possess enhanced biological activities compared to the all-trans isomer. Higher plasma levels of *cis*-lycopene have been associated with improved endothelial

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Table 1. Ingredients of lycopene containing treats.[a]

	Lycopene dose (mg/kg BW)			
Ingredient (per rat)	Control (0)	Low (0.05)	Mid (0.35)	High (2.6)
"Moonglow" tomato powder (mg)	0	25	175	1301
Peanut butter + honey (2:1; mg)	600	575	625	699
Total weight of a treat mixture per day (g)	0.6	0.6	0.8	2

[a]Ingredients were mixed daily to prepare the appropriate dose in mg/kg BW of rats. The amount of peanut butter + honey increased with increasing tomato powder to make it more palatable to rats and to ensure even mixing of tomato powder.

function and a reduced risk of cardiovascular diseases (Gajendragadkar *et al.* 2014). Additionally, the antioxidant properties of *cis*-lycopene may contribute to a lower cancer risk, including inhibition of prostate cancer cell proliferation (Holzapfel *et al.* 2013) and superior UV protection, which can help reducing the risk of sunburn (Stahl and Sies 2012).

Almost 90% of lycopene in red tomatoes is present in all-*trans*-isomeric form, whereas 90% of lycopene in orange heirloom tomatoes is in a *cis*- form, mainly in tetra-*cis*- form, which is also known as prolycopene (Unlu *et al.* 2007; Cooperstone, Francis and Schwartz 2016). However, rat studies have only been conducted using lycopene from conventional red tomatoes or synthetic lycopene in all *trans*- isomeric forms. We hypothesized that consumption of "Moonglow" tomatoes in small doses could be effective in producing beneficial levels of plasma lycopene while increasing lycopene accumulation in the liver, in rats. Therefore, the main objectives of the present study were to identify the daily dose of lycopene from "Moonglow" tomatoes, and the time period required to achieve a physiologically relevant level of lycopene in the plasma and to determine whether the *cis*- and *trans*- isomer ratios were altered after digestion, absorption, and metabolism in rats.

Materials and methods

Tomatoes

Fresh ripe "Moonglow" tomatoes were provided by Mark Christensen, Heritage Food Crops Research Trust, Whanganui, New Zealand. Upon receipt, fresh tomatoes were cut into medium-sized pieces and stored at −20 °C prior to freeze-drying. Frozen tomatoes were freeze-dried (Cuddon FD18, Blenheim, New Zealand). Tomatoes were ground using a food processor (Kenwood 800 W, Havant, UK) into a fine powder and separately packed in zip-lock bags with inert nitrogen gas and again covered with aluminum resealable bags to protect from the light and kept at −20 °C until use.

Lycopene dose

"Moonglow" tomato powder in the appropriate dose and powdered commercial rat chow were mixed daily with smooth peanut butter (Sanitarium; New World, Palmerston North, New Zealand) and raw honey (provided by Horowhenua apiary H5206) to increase palatability and to form a solid treat that could be easily given to the rats for voluntary consumption. The control group received peanut butter and honey without tomato powder. Rats were trained to eat control treats for 2 days prior to the tomato treats. Low, mid, and high doses would equate to humans' intake of 0.5, 3, and 25 mg lycopene/day or 3, 24, and 180 g/day of fresh "Moonglow" tomatoes (Table S1).

Animals and diet

All animal procedures were carried out under the ethical approval obtained from Massey University Animal Ethics Committee (Protocol No: 18/40). Twenty-seven 8-week-old female Sprague-Dawley rats were obtained from Animal Resource Centre, Australia. Following importation, rats were quarantined for 1 month at the Small Animal Production Unit, Massey University (Palmerston North, New Zealand) according to the requirements of the Ministry of Primary Industries (MPI, New Zealand). Rats were weighed and transferred to clean standard plastic shoe-box cages with wood bedding upon arrival. Temperature and humidity were set at 22 °C and 45%-50%, respectively, with a 12-12 h light-dark cycle. All rats had *ad libitum* access to standard chow pellets and distilled water. Teklad Global 18% Rodent Diet, which is formulated to AIN 93 M specifications, was purchased through Fort Richards, Auckland, New Zealand. This diet contains 18.5% crude protein from wheat, corn, and soybean, and 6.2% fat from soybean oil, with an energy density of 13.0 kJ/g. A full list of ingredients is available via the Envigo.com website (Teklad 2018), although the full commercial formulation remains proprietary. Rats were monitored for their health and behaviors. A power analysis was carried out using PS (Power and Sample Size; Vanderbilt) based on published data for lycopene bioavailability studies for different species (Sicilia *et al.* 2005; Mills, Simon and Tanumihardjo 2007; Faisal, O'Driscoll and Griffin 2010). A sample size of 3-4 was necessary for a power of 0.8 to detect significant differences between groups when $P = .05$. Therefore, we selected $n = 3$ rats per group as we assessed 3 doses at a single time point, plus one dose at 6 time points. At the end of the quarantine period, 12 rats were individually housed in separate metabolic cages for study #1 (dose-response) and 15 rats were individually housed in shoe-box cages for study #2 (time-course). Rats were given a 2-day adaptation period in their cages with *ad libitum* chow diet and water. Following this period, "Moonglow" tomato feeding was initiated.

Animal trial 1 (dose-response)

Twelve ($n = 12$) 8-week-old female Sprague-Dawley rats were randomly assigned into 4 experimental groups ($n = 3$). Each rat was housed separately in a metabolic cage to facilitate a daily collection of urine and feces, which were weighed, placed into labeled tubes and stored at −20 °C until analysis. Four different groups were fed treats with "Moonglow" tomato powder containing total lycopene at a concentration of 0 (no dose), 0.05 (low dose), 0.35 (mid-dose), and 2.6 (high dose) mg/kg BW over 5 days (Table 1). Rats received one treat per day on days 1, 2, 3, 4, and 5 between 9 a.m. and 10 a.m. and feces and urine of the previous day were collected between 9 a.m. and 10 a.m. on the following day. On day 6, all rats were deeply anaesthetized between 9 a.m. and 11 a.m. with an intraperitoneal injection of 0.12 mL/100 g BW of acepromazine (2 mg/mL): ketamine (100 mg/mL): xylazine (10%): and sterile water = 2:5:1:2. Blood was collected from each rat by cardiac puncture into heparin sulphate-containing vacutainers. Euthanasia from exsanguination was confirmed with pneumothorax and the livers dissected, weighed, snap frozen and kept at −80 °C until further analysis. Blood samples were centrifuged at 3500 *g* for 10 min at 20 °C (Allegra 64R, Beckman Coulter, Australia) to obtain the plasma.

Animal trial 2 (time-course)

Fifteen (n = 15) 8-week-old female Sprague-Dawley rats were housed separately in shoe-box cages and fed with lycopene mid-dose (0.35 mg/kg BW) once daily as above. At selected time points (n = 3 rats per time point), animals were euthanized, and blood and liver were collected and processed as above. Rats were acclimatized for 2 weeks prior to the experimental feeding period.

Extraction of carotenoids from tomatoes

Carotenoids were extracted under minimum light, using the method previously described (Brown *et al.* 2004). Briefly, 5 g of tomato powder was added to a 50 mL plastic test tube. This was mixed with a mixture of 500 mg Na_2CO_3, 5 g anhydrous Na_2SO_4 with 20 mL of tetrahydrofuran (THF): methanol (2:1). Samples were shaken in a genogrinder (2010 Geno/Grinder) at 183.3 rad/s for 4 min. After 60 min of incubation in the dark, samples were centrifuged at 1620 g for 10 min (Eppendorf centrifuge 5804, with rotor A-4) and the supernatant was collected into a 50 mL glass bottle. The extraction process was repeated on the remaining solid fraction and the supernatants were pooled together, and the total volume was recorded. Extracts were analyzed using ultra-high-performance liquid chromatography (uHPLC)-DAD.

Carotenoid extraction from plasma and urine of rats

Plasma and urine carotenoids were extracted using the methods previously described (Kopec *et al.* 2010; Cooperstone *et al.* 2017). Briefly, plasma (500 µL) or urine (1 mL) were added to the same volume of ethanol with 0.1% Butylated hydroxy toluene (BHT) and 0.5 mL of saturated NaCl. The mixture was vortexed for 15 s, followed by the addition of 2 mL of 10:6:7:7 (v/v/v/v) hexane:ethanol:acetone:toluene (HEAT). Mixture was vortexed again for 15 s and centrifuged at 1000 g for 5 min at −20 °C (Allegra 64R, Beckman Coulter, NSW, Australia). The top layer was transferred to a new Kimax tube using a soda lime pasteur pipette. Each biological sample was extracted thrice. The extracts were dried under nitrogen gas and stored at −20 °C until analysis, which was carried out within 2 days. Samples were re-dissolved in 75 µL of THF:methanol (1:3) before analysis.

Carotenoid extraction from liver and feces of rats

Liver and feces carotenoids were extracted using the methods previously described (Boileau, Clinton and Erdman Jr 2000; Zaripheh *et al.* 2003). Briefly, the frozen livers and feces were freeze-dried using a freeze dryer (Cuddon FD18, Blenheim, New Zealand). Freeze-dried livers/feces were crushed to a powder using a porcelain mortar and pestle. 0.1 g of freeze-dried liver/feces were dissolved in 3 mL of KOH (60%)/ethanol (1:5) solution containing 1 g BHT/L. Samples were vortexed and kept in a water bath at 60 °C for 30 min for complete saponification. Samples were again vortexed after adding hexane (3 mL) and distilled water (1 mL) and centrifuged at 1000 g for 5 min (Allegra 64R, Beckman Coulter, NSW, Australia). The top layer was collected as mentioned previously. Samples were extracted thrice, and dried extracts were stored at −20 °C until analysis, which was carried out within 2 days. Samples were re-dissolved in 100 µL of THF:methanol (1:3) before analysis by HPLC. Weights of liver and feces were measured before and after freeze-drying. Lycopene concentration was measured in 0.1 g of freeze-dried liver/feces and back calculated for fresh liver/feces weight.

Ultra-high-performance liquid chromatography

Analysis of carotenoids was performed at Plant and Food Research, Palmerston North, New Zealand. Extracts of "Moonglow" tomatoes and rat biological samples were analyzed for their carotenoid composition using uHPLC-DAD. The Ultimate™ 3000 HPLC system (Dionex) consisted of an Ultimate™ HPG-3400RS rapid separation binary pump (Dionex), Ultimate™ WPS-3000RS auto sampler, and the Ultimate™ DAD -3000RS detector (Dionex). A 150 × 2.1 mm, 2.6 µm pore-size C30 Accucore carotenoid column was used for the separation of carotenoids. The system was flushed with 100% acetonitrile before each sequence. Solvent A consisted of methanol/milliQ water (50:50, v/v), and solvent B consisted of methanol/isopropanol/methyl tetra butyl ether/milliQ water (100:100:80:2, v/v) with a flow rate 0.4 mL/min. Column temperature was set at 40 °C with a CH-150 column heater (ESA). Acetone was used as a needle wash solution between each injection. The linear gradient was applied as follows: 60% B to 100% B over 12 min, held at 100% B over the next 4 min, to 60% B for 0.5 min, held at 60% B for the last 3.5 min.

Data processing

Data processing was performed using Chromeleon™ 7.2 SR4 software (ThermoScientific™). All-*trans*-lycopene was identified based on the retention time of the standard and its spectral characteristics and quantified by the standard curve created. Tetra-*cis*- isomer was identified by its distinctive absorption spectrum at 435 nm. Since there are no commercial standards available for tetra-*cis*-lycopene, the quantification was done through the calculation of the response factor using extinction coefficients (Britton, Liaaen-Jensen and Pfander 1994) of both tetra-*cis*- and all-*trans*-lycopene to yield a relative slope (Cooperstone, Francis and Schwartz 2016) (see formula below). *Cis*-lycopene isomers except tetra-*cis*- were collectively quantified as other-*cis*-lycopene, equivalent to all-*trans*- as done in other studies (Moraru and Lee 2005; Fröhlich *et al.* 2007).

$$Extinction\ coefficient\ ATLyc\ \ (436nm) = \left(\frac{Average\ ATlyc\ area\ \ (436\ nm)}{Average\ ATLyc\ area\ \ (470\ nm)}\right) x \times Extinction\ coefficient\ of\ \ ATlyc\ \ (470\ nm)$$

$$Response\ factor = \left(\frac{Extinction\ coefficient\ of\ TClyc\ \ (436\ nm)}{Extinction\ coefficient\ of\ ATlyc\ \ (470\ nm)}\right)$$

Additional variables calculations

$$Lycopene\ retention\ in\ the\ body = \left(\frac{Lycopene\ intake - Lycopene\ in\ feces}{Lycopene\ intake}\right) * 100$$

Statistical analyses

Results are presented as means with standard error of the mean (means ± SEM). All statistical analyses were conducted using SPSS statistical software version 25. All the data were tested for normality using the Shapiro-Wilk test and the homogeneity of group variances was assessed by Levene's test. The differences between group means were analyzed using one-way analysis of variance (ANOVA) followed by a post-hoc Tukey test. A difference was considered statistically significant when $P < .05$.

Table 2. Lycopene isomer composition after 5 days supplementation of "Moonglow" tomato, in rats.[1]

Lycopene isomers	Plasma (μmol/L)			Liver (μmol/kg)		
	Low	Mid	High	Low	Mid	High
Cis- lycopene	0.06 ± 0.01^{c}	0.60 ± 0.02^{b}	1.84 ± 0.06^{a}	1.18 ± 0.09^{c}	13.15 ± 1.02^{b}	109.36 ± 7.40^{a}
All-*trans*- lycopene	n. d.	n. d.	0.03 ± 0.00	0.40 ± 0.07^{c}	2.42 ± 0.50^{b}	12.57 ± 1.16^{a}

[1]Values are means ± SEM, $n = 3$. Statistical analysis was performed by using one-way ANOVA and post-hoc Tukey tests. Different superscripts (a,b,c) within liver groups or within plasma groups are significantly different at $P < .05$. n.d. indicates not detected.

Table 3. Lycopene concentrations in feces, urine, and as a % of daily dose*

	Control	Low	Mid	High
Body weight (g)	230.5 ± 5.8	229.4 ± 3.1	228.9 ± 3.6	229.8 ± 2.8
Lycopene dose (mg/kg BW)	0.00	0.05	0.35	2.6
Lycopene dose (nmol/day)	0.00	22.6	158.3	1174.5
Lycopene in feces (nmol/day	0.00	10.64 ± 1.17^{c}	70.70 ± 9.48^{b}	635.43 ± 48.06^{a}
Percent lycopene in feces/daily dose[2]	0.00	43.9 ± 4.9	43.1 ± 5.8	52.5 ± 4.0
Lycopene in urine (nmol/day)	0.00	0.27 ± 0.05	0.31 ± 0.04	0.35 ± 0.05
Percent lycopene in urine/daily dose[2]	0.00	1.20 ± 0.24^{a}	0.19 ± 0.02^{b}	0.03 ± 0.003^{c}

[1]Values are means ± SEM, $n = 3$. Statistical analysis were performed using one-way ANOVA and post-hoc Tukey tests. Data with different superscript letters (a,b,c), in each column, are statistically significantly different at $P < .05$. [2] Lycopene excretion via feces or urine as a proportion of rats' daily intake (days 2-5).

Results

Analysis of lycopene levels in "Moonglow" tomatoes

Peaks of the "Moonglow" tomato chromatogram were matched against available standards of lutein, β-carotene, and all-*trans*-lycopene (Figure S1). "Moonglow" tomatoes are rich in tetra-*cis*-lycopene isomers. Other than the tetra-*cis*, phytoene, phytofluene, and carotene were identified based on the unique carotenoid profile of tangerine tomatoes. Their identification was confirmed using their specific spectral characteristics, with phytoene exhibiting a maximum absorption at 286 nm and phytofluene at 348 nm and carotenes at 400 nm, as previously described in the literature (Britton, Liaaen-Jensen and Pfander 1994; Cooperstone, Francis and Schwartz 2016) (Figures S2 and S3 and Table S2). Smaller amounts of other-*cis* and all-*trans*-lycopene were identified and quantified by using the all-*trans*- calibration curve as discussed in other studies (Moraru and Lee 2005; Ishida 2007). The total lycopene content in fresh "Moonglow" tomatoes was measured at 6.76 mg/100 g fresh weight (FW), consisting of tetra-*cis* lycopene (6.57 mg/100 g FW), all-trans lycopene (0.03 mg/100 g FW), and other *cis*- isomers (0.16 mg/100 g FW). In the freeze-dried "Moonglow" tomatoes, the total lycopene content was 4.06 mg/100 g freeze-dried weight (FDW), comprising tetra-*cis* lycopene (3.94 mg/100 g FDW), all-trans lycopene (0.018 mg/100 g FDW), and other *cis*-isomers (0.096 mg/100 g FDW). Thus, the tested "Moonglow" tomatoes contained >97% lycopene in its *cis*-isomeric form.

Dose-dependent plasma and liver lycopene concentrations

Plasma lycopene concentrations at low, mid, and high doses were 0.06, 0.60, and 1.87 μmol/L respectively, and the values were significantly different ($P < .05$). Among total lycopene in high doses, 96% was in the form of tetra-*cis*- whereas 3.4% was from all-*trans*- and other-*cis*- isomers. In contrast to plasma, liver accumulated much higher quantities of lycopene in all-*trans*- and *cis*- isomeric forms (Table 2). The total lycopene concentrations in the liver were 1.59, 15.6, and 121.9 μmol/kg for low, mid, and high doses respectively. Liver lycopene also showed a dose response pattern with increasing dose. Liver contained more than 70% of lycopene in *cis*- isomeric forms (tetra-*cis*- and other-*cis*-) from all 3 doses, with the remainder being all-*trans*-. The proportion of *cis*- isomers in the liver increased significantly ($P < .05$) with the increase in dietary lycopene intake. Total *cis*-lycopene concentration was 75% for rats fed 0.05 mg/kg, 84% for rats fed 0.35 mg/kg, and 90% for those fed 2.6 mg/kg. The all-*trans*-lycopene concentration was 25% for rats fed 0.05 mg/kg, 16% for rats fed 0.35 mg/kg, and 10% for those fed 2.6 mg/kg (Table 2). Plasma and liver chromatograms are provided in Figure S4a and b, respectively.

Lycopene excretion

In this study, we noticed that the high-dose rats failed to eat the majority of their dose on day 1. This could be due to rats' natural inclination to not fully consume a new feed. To be consistent with all 3 groups, the day 1 data were excluded from all 3 doses and only day 2-5 data were considered during the calculation of lycopene retention. Minimal lycopene was excreted in the urine. The majority of lycopene was found in feces where the means over 4 days were 10.6, 70.7, and 635.4 nmol/day for low, mid, and high doses, respectively (Table 3). The amount of lycopene in feces and urine as a proportion of rats' daily intake was also calculated (Table 3). Lycopene in feces as a percentage of daily intake increased over time in all 3 doses. The mean amount of lycopene over time was significantly different amongst the 3 doses. At the end of the study period, 43%-53% of lycopene from rats' daily intake was found in feces in all 3 doses (Table 3). Mean fecal recovery of lycopene as a percentage of dose was not significantly different between the 3 doses and this suggests that regardless of the dose, nearly half of the administered lycopene was recovered in feces.

Only minute amounts of lycopene were detected in the urine of all doses. The amount of lycopene in urine as a proportion of daily intake was 1.2%, 0.19%, and 0.03% for low, mid, and high doses, respectively. In contrast to the feces, the mean amount of lycopene over time was not significantly different in urine among the 3 doses, although the values did increase with increasing dose.

Time-course of lycopene accumulation in rats

This study was designed to evaluate the time-course of a daily feeding of mid-dose (0.35 mg/kg BW) of "Moonglow" tomato on total lycopene concentration in plasma and liver, over 5 con-

Table 4. Lycopene isomer composition after "Moonglow" tomato supplementation, in rats.[1]

Day	Plasma (µmol/L)		Liver (µmol/kg)	
	Cis- isomers	All-*trans*- isomers	*Cis*- isomers	All-*trans*- isomers
1	0.13 ± 0.01[c]	n.d.	2.68 ± 0.29[c]	0.56 ± 0.06[b]
2	0.31 ± 0.06[b]	n.d.	6.24 ± 0.96[bc]	1.71 ± 0.42[ab]
3	0.35 ± 0.04[b]	n.d.	8.33 ± 1.62[b]	1.39 ± 0.30[ab]
4	0.42 ± 0.02[ab]	n.d.	13.27 ± 0.65[a]	2.27 ± 0.34[a]
5	0.60 ± 0.02[a]	n.d.	13.15 ± 1.02[a]	2.42 ± 0.50[a]

[1]Values are means ± SEM, $n = 3$. Statistical analysis was performed using one-way ANOVA and post-hoc Tukey tests. Data with different superscript letters (a,b,c) within each column are statistically significantly different at $P < .05$. n.d. indicates not detected.

Table 5. Lycopene retention after "Moonglow" tomato supplementation, in rats.[1]

Day	Lycopene retention in the body (nmol)[2]	Lycopene retention in the liver (nmol)[3]	Percent lycopene retention in the body[4]
1	93.7 ± 15.00[e]	9.023 ± 1.85[c]	9.81 ± 2.77
2	268.65 ± 24.20[d]	21.32 ± 3.01[b]	7.85 ± 0.46
3	422.87 ± 12.66[c]	26.99 ± 5.62[ab]	6.34 ± 1.19
4	591.34 ± 22.39[b]	40.98 ± 1.51[a]	6.94 ± 0.23
5	732.59 ± 2.08[a]	43.84 ± 3.95[a]	5.98 ± 0.53

[1]Values are mean ± SEM, $n = 3$. Statistical analysis was performed using one-way ANOVA and post-hoc Tukey tests. Data with different superscript letters (a,b,c) within each column are statistically significantly different at $P < .05$. [2] Lycopene retention in the body is the difference between daily dose of lycopene (ie lycopene intake) and the amount of lycopene present in feces. [3]Lycopene retention in the liver is the amount of lycopene measured in the liver. [4]Percent lycopene retention in the body is the ratio between lycopene retention in the body and the lycopene in the liver.

secutive days. Plasma lycopene concentration increased significantly through the 5-day supplementation period and did not reach a plateau. Lycopene accumulated significantly in the livers of rats over time up to day 4 and then reached a steady-state level ($P < .05$). Only tetra-*cis*-lycopene was detected in the plasma each day. Liver accumulated both *cis*- and *trans*- isomers, but there was around 4-6 times more *cis*-lycopene each day compared to all-*trans*- (Table 4).

Since our study 2 evaluated the time-course of lycopene accumulation, we also calculated the amount of lycopene retained in the body at each time point following supplementation of mid-dose and the liver accumulation of retained lycopene (Table 5). Retention of lycopene was calculated each day using the difference between accumulated daily dose of lycopene fed to rats and the total amount excreted in feces and urine. Amount of lycopene retained in the body was significantly increased with the time. Percent lycopene accumulation in the liver did not significantly differ throughout the study period (Table 5).

Discussion

As hypothesized, our mid-dose (0.35 mg/kg BW) resulted in a plasma concentration of 0.42 µmol/L after only 4 days of feeding, which is similar to the reported physiological beneficial concentration in humans (Walfisch *et al.* 2003; Fielding *et al.* 2005; Mackinnon 2011; Hanson *et al.* 2018). Our results also showed a clear dose-response of plasma and liver lycopene when doses increased from 0.05 to 2.6 mg/kg body weight. Liver lycopene accumulation was significantly higher ($P < .05$) at high doses than other 2 doses. The 3 doses used in this study achieved several fold higher plasma and liver lycopene concentrations within a 5-day period compared to similar rat studies with lycopene in all-*trans*-isomeric form. For example, the mid-dose of "Moonglow" achieved a *cis*-lycopene plasma concentration after 5 days comparable to that measured in a similar time frame with a 70-fold higher dose of all-*trans*- (Zaripheh *et al.* 2003). Similarly, the mid-dose of "Moonglow" after 5 days achieved a *cis*-lycopene concentration in liver comparable to that measured in rats fed 14-fold (Boileau *et al.* 2000) and 13-fold (Ferreira *et al.* 2000) higher amounts of all-*trans*- for 8-9 weeks. This was somewhat expected, as *cis*-lycopene has been shown to be approximately 8.5 times more bioavailable than all-*trans*- (Cooperstone 2015).

Existing research suggests that there is no significant difference between *cis*- and trans-lycopene isomers in delivering overall health benefits. Both isomers have been shown to contribute to reduced oxidative stress and improved cardiovascular health (Shi and Maguer 2000). However, some recent studies suggest elevated plasma levels of *cis*-lycopene have been associated with enhanced endothelial function and a decreased risk of cardiovascular diseases (Gajendragadkar 2014). Furthermore, the antioxidant properties of *cis*-lycopene may contribute to cancer prevention, including the inhibition of prostate cancer cell growth (Holzapfel 2013), and offer improved protection against UV damage, helping to reduce the likelihood of sunburn (Stahl and Sies 2012).

The main objectives of the present study were to identify the daily dose of lycopene from "Moonglow" tomatoes and the time period required to achieve a physiologically relevant level of lycopene in the plasma and to determine whether the *cis*- and *trans*- isomer ratios were altered after digestion, absorption, and metabolism in rats. This study was part of a larger trial evaluating the effects of lycopene on bone loss using an ovariectomized (OVX) rat model. Female rats were specifically chosen because they are essential for the OVX model, which accurately mimics postmenopausal conditions. While ferrets are considered suitable models for carotenoid absorption studies due to their physiological similarities to humans in carotenoid metabolism (Lee *et al.* 1999), they are not established models for studying bone-related diseases such as osteoporosis (Jee and Yao 2001). Moreover, practical considerations such as availability, manageability, and affordability often influence the selection of animal models, further supporting the use of rats in this study (Lee 1999).

Several rat studies have demonstrated that plasma lycopene concentrations in rats are similar to those observed in human trials (Boileau, Clinton and Erdman Jr 2000; Ferreira *et al.* 2000, Boileau and Erdman Jr 2002). Interestingly, the plasma lycopene achieved in our study was similar to the reported human studies even at the low dose of feeding (Gerster 1997; Mackinnon 2011). The isomeric composition of lycopene differed in plasma and the liver of rats supplemented with “Moonglow” tomato powder for 5 days. The proportions of *cis*-lycopene in the liver after 5 days of “Moonglow” feeding were 75%, 84%, and 90% for low, mid, and high doses, respectively. These percentages matched a recent finding where feeding *cis*- isomers of lycopene at a dose of 5 or 10 mg/kg BW of mice produced 81.6% or 81.0% of total *cis*- isomers and 18.4% or 19.0% all-*trans*-lycopene in the liver after 4 weeks of supplementation (Honda *et al.* 2020). This study further showed that the feeding of a diet rich in *cis*- isomers could produce 3 times higher levels of total lycopene in the liver compared to all-*trans*-lycopene. It suggests that the consumption of *cis*- isomers will enhance lycopene accumulation in the liver. Lycopene absorption from dietary sources is limited (10%-30%), leaving over 70% unabsorbed (Stahl and Sies 1992). The higher bioavailability of *cis*-isomers becomes significant, enabling more effective uptake despite absorption constraints. While their functional benefits are similar, the greater bioavailability of *cis*- isomers supports their prioritization in dietary sources to achieve optimal tissue levels. For lycopene to exert its health benefits, it must be released from the food matrix and solubilized into mixed micelles before absorption (Cooperstone 2015). *Cis*- isomers, being less prone to crystallization, more soluble in oil, and preferentially micellarized, are absorbed more efficiently by intestinal cells (Ishida 2007; Cooperstone 2015). This structural advantage enhances the bioavailability and distribution of *cis*-lycopene across tissues (Cooperstone 2015).

Despite the “Moonglow” tomato containing 97% of lycopene in *cis*- isomeric form, 10%-25% of lycopene accumulated in the liver was all-*trans*- regardless of dose. In the single comparative study available assessing the isomeric composition of lycopene in diet vs liver, intake of lycopene with 97% *cis*- isomers similarly resulted in liver lycopene of 81% *cis*- and 19% all-*trans*- isomers (Honda 2020). Part of the reason could be that a diet high in *cis*-lycopene may lead to its conversion into more stable isomeric forms, such all-*trans*- or 5-*cis*-lycopene, during absorption (Richelle 2012; Honda 2020). Another possible explanation is that the incorporation of fat into the diet can increase the absorption of all-*trans*- lycopene to the body. In our study, peanut butter was used as a source of fat containing a high amount of unsaturated fatty acids which can be preferably incorporated into lipoproteins (Roodenburg *et al.* 2000; Unlu 2007). Therefore, it possibly could facilitate the absorption of all-*trans*- lycopene. Further, the metabolism of lycopene isomers into apo-lycopenals in the liver also could change the isomeric composition in the liver (Gajic *et al.* 2006). We did not measure lycopene metabolites, which was a limitation of this study.

Lycopene excretion has been shown to occur mainly through feces while only a minute amount is eliminated in the urine (Zaripheh 2003). Minute amounts of some carotenoids absorbed after digestion could also be excreted through sloughing of keratinized skin cells and expired air (Olson 1994). The percentage of administered doses found in urine showed an inverse relationship with the doses; however, the concentration of lycopene in urine did not differ significantly between groups and the amount of lycopene excreted by this route was minimal. The 3 doses used in our study did not show significant differences in the proportions excreted from each dose. Similarly, rats fed lycopene at 0.2 and 2 mg/kg BW showed no significant differences in the amounts recovered in feces (McClain and Bausch 2003). We chose our 3 doses based on the reported bioavailability of *cis*-lycopene, and therefore our selected doses were several times lower than reported doses in the literature that have shown dose-dependent saturation (Stahl and Sies 1992; Diwadkar-Navsariwala *et al.* 2003). Moreover, independent of the dose administered, lycopene accumulation can be very specific to the subjects tested. For instance, regardless of the dose, there are some people who are high accumulators while others are low accumulators of lycopene, and this may be true in rats as well. Therefore, inter-individual variation may affect lycopene absorption in the body (Diwadkar-Navsariwala 2003). Lycopene in urine was minimal overall. The amount of lycopene in urine did not differ between lycopene doses, but the proportion of lycopene doses excreted in urine was significantly reduced with the high lycopene dose compared to the lower doses. This may reflect the fact that we measured total lycopene recovered in urine but not the metabolites of lycopene. Lycopene is rapidly metabolized into polar metabolites and these are excreted in urine (Ross *et al.* 2011). It is likely that the high dose of lycopene resulted in more lycopene metabolic products in the urine, and this may be of interest in future to explore.

We observed that total lycopene accumulation increased in both plasma and liver daily over time. Liver lycopene reached a plateau after 4 days of feeding whereas plasma lycopene continued to rise. Porrini *et al.* studied the absorption of lycopene in humans from daily intake of raw tomatoes containing 16.5 mg lycopene for 9 days and showed a steady daily increase of plasma lycopene up to day 7 when it peaked at ∼0.58 µmol/L, after which it declined (Porrini, Riso and Testolin 1998); in comparison, plasma lycopene concentration in our mid-dose rats was 0.6 µmol/L on day 5. These concentrations are similar enough, and thus it is likely that a longer feeding period would not have achieved a significant increase in plasma lycopene in the rats. In other studies, plasma lycopene was found to stabilize at 0.58-0.72 µmol/L in gerbils fed 20 mg/kg BW lycopene for 20 days (Huang, Chuang and Hu 2006), at 0.78-0.98 µmol/L in dogs fed 30 mg/kg BW all-*trans*-lycopene for 28 days (Korytko *et al.* 2003), and at 0.602 µmol/L in postmenopausal women supplemented with 30 mg lycopene per day for 4 months (Mackinnon 2011). Another human trial found plasma lycopene plateaued at 0.75 µmol/L after 2 weeks of supplementation of lycopene at 25 mg/day (Richelle *et al.* 2002).

This is the first report on the daily accumulation of lycopene in the liver in any animal model. We found that lycopene stored in the liver increased daily until day 4, at which point the levels plateaued. Approximately 6%-8% of the lycopene retained in the body was present in the liver each day for 5 days of *cis*-lycopene rich “Moonglow” tomato feeding. In mice given dose-matched supplementation with *cis*- isomers of lycopene vs all-*trans*- for 4 weeks, the former resulted in 3-fold more liver lycopene, attributed to its higher bioavailability (Honda 2020). It is thus likely that consumption of “Moonglow” tomato compared to red tomato would result in higher liver stores and greater health benefits.

In conclusion, this study shows that lycopene from “Moonglow” tomatoes is highly bioavailable and even low doses result in measurable lycopene isomers in plasma and liver. For the first time, we report daily lycopene accumulation in the liver of rats following intake of *cis*- isomers from “Moonglow” tomato, with nearly 6%-8% of the lycopene retained in the body being present in the liver on each day of feeding. Based on these results, we conclude that consumption of even small amounts of “Moonglow” tomatoes by humans is likely to result in beneficial plasma levels of lycopene. In future animal model and human intervention studies, both absorption kinetics and the health benefits of *cis*- lycopene should be examined. It will also be of interest to carry out direct comparisons between red and "Moonglow" tomatoes delivered in matching formats and doses.

Supplementary material

Supplementary material is available at *Bioscience, Biotechnology, and Biochemistry* online.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Author contribution

U.S.W.: Conceptualization, methodology, formal analysis, investigation, data curation, writing—original draft preparation, writing—review and editing. F.M.W.: Conceptualization, methodology, investigation, resources, writing—review and editing, supervision, funding acquisition. A.Z.-G.: methodology, writing—review and editing, supervision. M.C.K.: Conceptualization, methodology, resources, writing—review and editing, supervision, funding acquisition. J.A.H.: Conceptualization, methodology, resources, writing—review and editing, supervision, project administration, funding acquisition. All authors have read and agreed to the published version of the manuscript.

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Disclosure statement

The authors declare no conflicts of interest related to this manuscript. The research was conducted independently, and there were no financial or personal relationships with individuals or organizations that could influence the work reported in this manuscript. Any funding sources or institutional support received for this research are appropriately acknowledged in the manuscript.

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