Effects of ingestion of tomatoes, tomato juice and tomato purée on contents of lycopene isomers, tocopherols and ascorbic acid in human plasma as well as on lycopene isomer pattern

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Tomatoes are an important part of the diet. Lycopene, the predominant carotenoid in tomatoes, is hypothesised to mainly mediate the health benefits of tomato products. Anticancer activity of tomato products and lycopene has been suggested by numerous studies. The aim of the present study was to investigate the effect of ingestion of three different tomato-based foodstuffs on plasma contents of lycopene, tocopherols and ascorbic acid. Because isomers of lycopene may have different biological activities, a special interest was to look how the lycopene isomer pattern is changed depending on the matrix of tomato products. Following a 2-week depletion phase volunteers ingested 12.5 mg lycopene/d for 4 weeks comprising tomatoes, tomato juice or tomato purée. The basal levels of lycopene in plasma were comparable for all groups and decreased significantly during the 2 weeks of depletion to approximately half of the basal values. Following intervention, plasma lycopene concentration increased significantly. Conversely, supplementation did not significantly affect levels of tocopherols and ascorbic acid in plasma. Regarding isomers of lycopene, the (Z)-lycopene/(all-E)-lycopene plasma isomer ratio was significantly changed during the study for all groups. A remarkable enrichment of the relative contents of (Z)-lycopene was observed during the depletion period, which supports the hypothesis that lycopene (Z)-isomers are formed within the human body after ingestion of (all-E)-lycopene. After dietary intervention with lycopene-rich products the isomer ratios returned to those observed at the start of the study. Further investigations will clarify the process of isomerisation in more detail.

Tomato products: (all-E)-Lycopene: Lycopene (Z)-isomers: Ascorbic acid: Tocopherols: Human bioavailability

Several epidemiological studies have indicated a beneficial effect of tomato consumption in the prevention of some major chronic diseases, such as some types of cancer (Giovannucci et al. 2002) and CVD (Klipstein-Grobusch et al. 2000). One of the major phytochemicals in tomato products contributing to the prevention of cancer is lycopene. Reports from epidemiological studies, studies in animals and cell-culture experiments have suggested that lycopene has anticancerogenic properties (Rao & Agarwal, 1999; Etmian et al. 2004; Tang et al., 2005). In addition to its antioxidant properties (DiMascio et al. 1989; Böhm et al. 2002), lycopene has also been shown to induce cell–cell communication (Zhang et al. 1991; Stahl et al. 2000), activate phase II enzymes (Breinholt et al. 2000), inhibit tumour cell proliferation (Levy et al. 1995), repress insulin-like growth factor receptor activation (Karas et al. 2000), and improve anti-tumour immune responses (Clinton, 1998). The mechanisms by which lycopene might exert its biological activities are still unknown.

The general structure of lycopene is an aliphatic hydrocarbon with eleven conjugated carbon–carbon double bonds, making it soluble in lipids and red in colour. Being acyclic, lycopene has no vitamin A activity. Recent investigations have shown that lycopene derivatives could activate retinoid receptors. However, the physiological significance has to be shown in future studies (Sharoni et al. 2004). Lycopene from tomatoes and tomato-based foods exists predominantly in the (all-E)-configuration, the thermodynamically most stable form (Porrini et al. 1998). In contrast, various (Z)-isomers account for over 50% of blood lycopene and for over 75% of tissue lycopene (Clinton et al. 1996; Ferruzzi et al. 2001). The processes that influence isomer patterns and the mechanisms of interconversion are still an essentially unexplored area of research. Isomerisation of lycopene may have significant consequences since the large three-dimensional differences between these geometric isomers may influence their pharmacological properties (Holloway et al. 2000). Recent investigations using the Trolox equivalent antioxidant capacity assay have shown significantly different antioxidant activity for lycopene isomers depending on the geometrical structure (Böhm et al. 2002).

The aim of the present study was to explore the inter-relationships among the intake of different commonly consumed tomato products (tomatoes, tomato juice, tomato purée), plasma lycopene isomer profiles and plasma levels of ascorbic acid and tocopherols. All volunteers were supplied with a daily dosage of 12.5 mg lycopene for 4 weeks after a 2-week diet low in lycopene.

Subjects and methods

Subjects and study design

Seventeen subjects (fourteen women and three men) ranging from 19 to 25 years with a BMI between 19 and 25 kg/m².
The main characteristics of the subjects participating in the study and composition of the supplemented tomato products (Mean values and standard deviations)

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Group</th>
<th>Tomato</th>
<th>Tomato juice</th>
<th>Tomato purée</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td>23.0</td>
<td>0.6</td>
<td>22.8</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td></td>
<td>61.7</td>
<td>5.4</td>
<td>62.7</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td></td>
<td>21.7</td>
<td>1.7</td>
<td>21.4</td>
</tr>
</tbody>
</table>

Table 1. The main characteristics of the subjects participating in the study and composition of the supplemented tomato products

Analysis of ascorbic acid

The content of ascorbic acid was determined by using a spectrophotometrical method according to Speitling et al. (1992). TCA (300 μl) was mixed with 200 μl of standard solutions (calibration straight line), plasma (which had been already prepared before storage at −80°C) or distilled water (blank reading value). The reaction mixture was vortexed and centrifuged (12 000 rpm; 5 min). Samples of 300 μl of the supernatant fraction were mixed with 100 μl dinitrophenylhydrazine-reagent (2 g/100 ml). The mixture was vortexed again, incubated at 60°C on a thermal shaker for 1 h and cooled on ice for 5 min. Then 400 μl sulfuric acid were added to the reaction mixture. After vortexing and keeping in the dark for 20 min, the mixture
was vortexed once again before spectrophotometrical analysis at 520 nm against the blank reading.

Tomatoes, tomato juice and tomato purée were analysed on their contents of ascorbic acid as recently described elsewhere (Gahler et al. 2003) by using the spectrophotometrical determination as mentioned earlier for the plasma samples instead of the HPLC determination described there.

**Analysis of tocopherols**

Plasma (500 µl) was extracted by adding 400 µl ethanol containing 0·1 % BHT. The mixture was vortexed for 30 s. After the addition of 400 µl n-hexane the mixture was vortexed again for 1 min and centrifuged at 14 000 rpm for 4 min. The extraction was repeated three times and the combined organic phases were evaporated to dryness under N₂ at 30 ± 1°C. The residue was dissolved in 1 ml of mobile phase, vortexed and centrifuged (14 000 rpm, 4 min). The supernatant fraction was analysed on a diol-column by using n-hexane–methyl tert-butyl ether (96:4, v/v) as mobile phase at a column temperature of 50°C with fluorescence detection (Balz et al. 1992). Plasma tocopherol concentration was calculated by means of peak areas of the respective standards: α-, β-, γ-, δ-tocopherols (Calbiochem, Darmstadt, Germany).

Tomato products were analysed on their tocopherol contents as recently described elsewhere (Seybold et al. 2004) by using the same HPLC method as mentioned earlier for the plasma samples.

**Statistical analysis**

Results are expressed as means and standard deviations. Differences between variables were tested for significance by using the one-way ANOVA procedure (Tukey) for the basal values and for all other results the general linear model for the two-way ANOVA procedure (SPSS for Windows, release 10.07 [June 2000; SPSS Inc., Chicago, IL, USA]), using a level of significance of P<0·05. Results were defined as ‘comparable’ if P>0·05.

**Results**

A representative HPLC chromatogram demonstrating plasma separation of lycopene isomers in human plasma is shown in Fig. 1. Results were calculated as total lycopene, including (all-E)-, (13Z)-, (5Z,9’Z)-, (9Z)-, (5Z,9Z)- and (5Z)-lycopene as well as any not yet identified (Z)-isomer of lycopene and the contents of the isomers separately. The contents of several isomers of lycopene are shown in Fig. 2. The lycopene concentrations of tomatoes, tomato juice and tomato purée used in the present study are presented in Table 1. (all-E)-Lycopene is the predominant isomer in each tomato product, accounting for 90–95% of total lycopene in tomatoes, 95–98% in tomato juice and 92–94% in tomato purée.

**Total lycopene**

Total lycopene plasma levels of the three groups of volunteers are shown in Fig. 3. Basal mean lycopene levels of all groups were in a comparable range (P>0·05) between 0·57 and 0·78 µmol/l. After the 2-week diet with low lycopene intake, the total plasma lycopene concentration decreased (P<0·05) to 45–62 % of the basal values. The total lycopene plasma levels were significantly enhanced (P<0·05) relative to the depleted state from 0·25 (sd 0·14) to 0·39 (sd 0·23) µmol/l after 1 week of supplementation with tomatoes. Tomato juice also led to significantly (P<0·05) increased lycopene plasma levels after 1 week of supplementation from 0·43 (sd 0·15) to 0·61 (sd 0·17) µmol/l. The total lycopene plasma levels remained nearly stable during the next 3 weeks of supplementation. Supplementation with tomato purée led to significantly enhanced (P<0·05) plasma levels of lycopene after 2 weeks of intervention (0·37 (sd 0·19) to 0·74 (sd 0·24) µmol/l). After 4 weeks of intervention with tomato products the increase of total lycopene in plasma was comparable (P>0·05) for the three food matrices investigated. The total lycopene plasma levels at T4 of all groups (0·53–0·81 µmol/l) were not significantly different (P>0·05) from the basal levels (T–2).

**Isomers of lycopene**

The plasma levels of the several isomers of lycopene are shown in Fig. 2. The two major lycopene isomers in plasma of all volunteers were (all-E)- and (5Z)-lycopene. Decreases and increases in contents of both (Z)- and (all-E)-isomers of lycopene led to changes in concentrations of total lycopene within all intervention trials. Looking at alterations of the concentrations of the different (Z)-isomers of lycopene, only the (13Z)-lycopene showed significantly lower concentrations in plasma after intervention with tomatoes compared with tomato juice and tomato purée. The other lycopene isomers did not show significant (P>0·05) differences among the three groups. The ratios of the sum of all evaluated lycopene (Z)-isomers:(all-E)-lycopene were used for assessment of isomer changes in plasma. The (Z)-lyкопене:(all-E)-lycopene isomer ratio was reversed during the study for all groups. The percentages of diverse lycopene isomers are shown in Table 2. Plasma isomer concentrations showed an approximately 60:40 ratio of (Z):(all-E) at the start of the study. After a 2-week depletion period during which the participants consumed a diet low in lycopene, the ratios had changed. A decrease in the (all-E)-configuration to approximately 30 % of total lycopene and a compensatory increase of the (Z)-isomers to 70 % was observed. After 4 weeks of dietary intervention with tomato juice (63 % (Z); 37 % (all-E)) and tomato purée (61 % (Z); 39 % (all-E)) isomer ratios returned to those
observed at the start of the study. After 4 weeks of intervention with raw tomatoes the (Z):(all-E) ratio was 50:50.

Ascorbic acid and tocopherols

The contents of the antioxidant vitamins ascorbic acid and tocopherols in plasma did not change significantly (P>0.05) during the depletion period and were not affected by 4 weeks of supplementation with tomatoes or tomato products (data not shown).

Discussion

In the present study, volunteers ingested 12.5 mg lycopene/d from tomatoes, tomato juice and tomato purée. This is approximately a tenfold higher dose than those described in the German National Food Consumption Survey (Pelz et al. 1998). This high lycopene amount was chosen to guarantee sufficient detection of minor compounds in plasma such as some (Z)-lycopene isomers. Furthermore, 145–320 g tomatoes, 94–101 g tomato juice and 25–28 g tomato purée daily are in accordance with consumable amounts of tomato products.

At the end of a 2-week depletion period with a diet low in lycopene, the total plasma lycopene concentration decreased significantly (P<0.05) to 53 % (range 45–62 %) of the basal values. Other publications have reported comparable plasma lycopene clearance rates (Böhm & Bitsch, 1999; Allen et al. 2003).

The daily consumption of commercially available tomatoes and tomato products rapidly and significantly increases blood lycopene concentrations. The present study showed
investigations is the daily dosage of lycopene, which is higher within the present trial (12.5 v. 5 mg/d). Higher intestinal absorption of lycopene from processed tomato products compared with unprocessed tomatoes was also described in other studies (Gärtner et al. 1997; Porrini et al. 1998; van het Hof et al. 2000). The first steps of the carotenoid absorption include disruption of the food matrix and the subsequent release of the carotenoids from this matrix and from protein complexes (Britton, 1995). A greater increase in plasma lycopene was demonstrated following consumption of homogenised tomatoes compared with whole tomatoes, indicating that lycopene from disrupted cells is more available for absorption (Shi & Le Maguer, 2000; van het Hof et al. 2000). In the present study, an increased bioavailability may have resulted due to cutting the tomatoes into small pieces. It is also known that intestinal absorption is strongly affected by the fat content of the diet, fats being essential for carotenoid extraction from the aqueous bulk of the food and the formation of mixed micelles via which the carotenoids are absorbed by enterocytes and transferred to the tissues via plasma lipoproteins (Borel et al. 1996; Parker, 1997). Some participants made a tomato salad from the fresh tomatoes and dressed it with oil. Therefore, it may be assumed that the tomato group consumed more fat than the groups ingesting tomato juice or tomato purée. For this reason, an increased lycopene bioavailability for tomatoes is possible. The type of lipids consumed may also influence carotenoid absorption (Stahl & Sies, 1992; Borel et al. 1996). Future studies are necessary to assess many of the complexities of lycopene bioavailability.

Lycopene exists in multiple isomeric forms. The majority (>90%) of lycopene in tomatoes and tomato products is (all-E)-lycopene. After ingestion of lycopene-containing food, (Z)-isomers constitute more than 50% of the total lycopene in human plasma. In the present study, (all-E)-lycopene (39–40%) and (5Z)-lycopene (27–34%) are the predominant

**Table 2.** Relative contents of lycopene isomers over time in subjects consuming daily portions of tomatoes or tomato products for 4 weeks after a 2-week initial depletion period

<table>
<thead>
<tr>
<th></th>
<th>T–2 (%)</th>
<th>T0 (%)</th>
<th>T1 (%)</th>
<th>T2 (%)</th>
<th>T3 (%)</th>
<th>T4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tomatoes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(all-E)</td>
<td>39·5</td>
<td>4·1</td>
<td>30·3</td>
<td>4·5</td>
<td>45·4</td>
<td>4·7</td>
</tr>
<tr>
<td>(13Z)</td>
<td>7·3</td>
<td>4·0</td>
<td>11·9</td>
<td>5·5</td>
<td>9·1</td>
<td>3·9</td>
</tr>
<tr>
<td>(Z), unidentified</td>
<td>9·0</td>
<td>2·7</td>
<td>10·1</td>
<td>2·2</td>
<td>13·1</td>
<td>2·0</td>
</tr>
<tr>
<td>(5Z,9Z) + (9Z) + (5Z,9Z)</td>
<td>10·0</td>
<td>2·4</td>
<td>11·7</td>
<td>3·2</td>
<td>8·7</td>
<td>1·4</td>
</tr>
<tr>
<td>(5Z)</td>
<td>34·2</td>
<td>4·5</td>
<td>36·0</td>
<td>6·5</td>
<td>23·7</td>
<td>3·6</td>
</tr>
<tr>
<td><strong>Tomato juice</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>(all-E)</td>
<td>39·2</td>
<td>4·6</td>
<td>30·5</td>
<td>5·6</td>
<td>34·1</td>
<td>5·1</td>
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<td>(13Z)</td>
<td>20·7</td>
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<td>22·3</td>
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<td>23·5</td>
<td>3·5</td>
</tr>
<tr>
<td>(Z), unidentified</td>
<td>6·5</td>
<td>2·4</td>
<td>7·6</td>
<td>3·5</td>
<td>8·9</td>
<td>3·0</td>
</tr>
<tr>
<td>(5Z,9Z) + (9Z) + (5Z,9Z)</td>
<td>6·2</td>
<td>2·9</td>
<td>7·5</td>
<td>2·8</td>
<td>7·2</td>
<td>2·7</td>
</tr>
<tr>
<td>(5Z)</td>
<td>27·5</td>
<td>3·8</td>
<td>32·1</td>
<td>3·2</td>
<td>26·3</td>
<td>2·3</td>
</tr>
<tr>
<td><strong>Tomato purée</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(all-E)</td>
<td>40·1</td>
<td>6·0</td>
<td>24·9</td>
<td>3·9</td>
<td>38·2</td>
<td>9·5</td>
</tr>
<tr>
<td>(13Z)</td>
<td>15·3</td>
<td>6·1</td>
<td>21·1</td>
<td>6·0</td>
<td>20·5</td>
<td>2·6</td>
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<tr>
<td>(Z), unidentified</td>
<td>7·7</td>
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<td>1·4</td>
</tr>
<tr>
<td>(5Z,9Z) + (9Z) + (5Z,9Z)</td>
<td>7·0</td>
<td>6·9</td>
<td>8·4</td>
<td>8·1</td>
<td>4·4</td>
<td>4·3</td>
</tr>
<tr>
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<td>3·4</td>
<td>36·6</td>
<td>4·9</td>
<td>31·2</td>
<td>9·9</td>
</tr>
</tbody>
</table>

For details of subjects and procedures, see p. 734.
Lycopene isomers after human intervention

By S. M. Tepper, T. Franke, L. R. Vernooij, R. K. van Duijnhoven, R. H. J. Kromhout, K. J. C. Vissers, M. F. Boelens, and J. P. W. Verhoef

isomers at baseline, a finding consistent with other reports (Clinton et al. 1996; Schierle et al. 1997; Holloway et al. 2000; Richelle et al. 2002). During the depletion period, a significant change in the (Z):(all-\(E\)) isomeric ratios from approximately 60% (Z), 40% (all-\(E\)) before the study to 70% (Z), 30% (all-\(E\)) after 2 weeks on a lycopene-free diet was observed. Comparable changes in the (Z):(all-\(E\)) ratios of lycopene in human plasma were described in another study. Hadley et al. (2003) showed a significant decrease of (all-\(E\))-lycopene as a percentage of plasma total lycopene isomers from 44·4 (SEM 1·2)% to 39·6 (SEM 1·2)%); whereas total (Z)-isomers increased from 55·6 (SEM 1·2)% to 60·4 (SEM 1·2)% during a 1-week washout period. The percentage of (all-\(E\))-lycopene also decreased after 3 weeks on a lycopene-free diet in a study by Edwards et al. (2003). Conversely, a study by Müller et al. (1999) did not find a significant difference in the (Z):(all-\(E\))-lycopene ratio during a 2-week washout period. This decrease in the relative proportion of (E)-lycopene of total lycopene in plasma may be a result of several simultaneous processes, including a more rapid clearance of (all-\(E\))-lycopene, a greater tissue uptake of (all-\(E\))-lycopene or conversion to (Z)-isomers in the human body. In addition, the possible mobilization of lycopene from tissue stores where lycopene is predominantly found in the cis form may contribute to a relative increase in the plasma (Z)-isomer pool.

After 4 weeks of intervention with tomato juice and tomato puree (with the exception of tomatoes) the (Z):(all-\(E\))-lycopene ratio returned to those observed at the beginning of the study. Other studies confirmed these findings. Holloway et al. (2000) reported that (all-\(E\))-lycopene increased to 40–45% of plasma lycopene after 2 weeks of supplementation with 21 mg lycopene/d comprising tomato paste. Similarly, the percentage of (all-\(E\))-lycopene increased significantly from 30–32 at baseline to 44–46 after 3 weeks of intervention with watermelon juice (Edwards et al. 2003). However, Hadley et al. (2003) observed a decrease of the relative contents of (5Z)-lycopene in a study where sixty volunteers ingested 23–55 mg lycopene/d comprising tomato products for 15 d. The observations suggest that maintaining a stable (all-\(E\):(Z)) isomers ratio in the blood requires continued dietary intake of the (all-\(E\)) form being predominant in food. It is also possible that lycopene exists in plasma as a mixture of (all-\(E\))- and (Z)-isomers of lycopene because this mixture is the thermodynamically most stable equilibrium of different geometric isomers.

Accumulating evidence in human subjects (Stahl & Sies, 1992; Gärtner et al. 1997; Boileau et al. 2002) and in animal models (Boileau et al. 1999) supports the hypothesis that (Z)-lycopene isomers are preferentially absorbed to (E)-lycopene. This may be the result of a greater solubility of (Z)-isomers in mixed micelles and a lower tendency to aggregate (Britton, 1995). A study from Re et al. (2001) reported that a high percentage of (Z)-lycopene isomers is present in tissues because it is better absorbed than (E)-lycopene from the gastrointestinal tract. Therefore, the increase in plasma concentrations of (Z)-isomers following administration of products containing lycopene is not solely related to the content of dosed (Z)-lycopene isomers. The elevated content of different (Z)-isomers in plasma may account for a longer residence time, which is in line with a longer half-life for (Z)-isomers compared with that of (all-\(E\))-lycopene (Cohn et al. 2002). Alternative explanations are isomerisation of systemic available (all-\(E\))-lycopene within the human body. Isomerisation of (all-\(E\))-lycopene to (Z)-lycopene is likely to occur during digestion (Re et al. 2001), but only after (all-\(E\))-lycopene is released from the food matrix, in which it is fairly stable (Nguien & Schwartz, 1998). The presence of acid in the stomach is perhaps the most plausible cause of (Z)-isomer formation, but this does not explain the diversity in the distribution of geometrical carotenoid isomers found in different organs of the body. A recent human intervention study showed that there was no significant (E)–(Z) isomerisation of lycopene in the human stomach. The fact that lycopene (Z)-isomers are poorly transported by the chylomicrons and thus poorly absorbed strongly suggested that a (E)–(Z) isomerisation of lycopene occurs in the human body at a post-enterocyte level (Tyssandier et al. 2003). Future investigations are necessary to assess whether: (1) (Z)-lycopene isomers are preferentially absorbed in human subjects; (2) (all-\(E\))-lycopene is converted into (Z)-isomers after absorption; (3) (Z)-isomers of lycopene mobilised from body stores to plasma or (all-\(E\))-lycopene is preferentially degraded in the plasma compared with (Z)-lycopene. It is supposed that a combination of several mechanisms occurs in the human body.

Regarding vitamin C and E, no significant differences were observed in the plasma contents of ascorbic acid and tocopherols (\(P > 0.05\)) during the entire study period, although both vitamins were ingested with the tomatoes and tomato products. Tyssandier et al. (2004) also did not detect any change in plasma ascorbic acid and tocopherols in a study in which subjects ingested 96 g tomato puree/d for 3 weeks. The plasma concentrations of these micronutrients are mainly correlated with the dietary intake of these compounds, with tomatoes and tomato products contributing a minor part.

In conclusion, ingestion of 12·5 mg lycopene/d for 4 weeks as tomatoes, tomato juice and tomato puree resulted in significantly increased plasma concentration of total lycopene. Under the conditions in the present study, lycopene appeared to be approximately equally bioavailable from the three commodities. Looking at alterations of the relative contents of the lycopene isomers, the (Z):(all-\(E\))-lycopene isomer ratio was reversed during the study for all groups. A remarkable enrichment of the relative contents of (Z)-lycopene was observed during the depletion period. After dietary intervention with lycopene-rich products the isomer ratio regained a state comparable with those observed at the beginning of the washout period. Further investigations will clarify the process of isomerisation of lycopene in more detail.

Acknowledgements

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plasma after four days of consumption. *J Nutr* 130, 1189–1196.
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