Xanthones in Mangosteen Juice Are Absorbed and Partially Conjugated by Healthy Adults

Chureeporn Chitchumroonchokchai, Kenneth M. Riedl, Sunit Suksumrarn, Steven K. Clinton, A. Douglas Kinghorn, and Mark L. Failla

Introduction

Mangosteen (Garcinia mangostana Lin.) is a tree indigenous to Southeast Asia and Indonesia and is also grown in Hawaii and Puerto Rico (1). Mangosteen fruit has a purple exterior with an edible soft white pulp characterized by a sweet, slightly acidic flavor and surrounded by a brown pericarp or hull. The pericarp of the mangosteen has been used in traditional Thai medicine to treat inflammation, infections, wounds, and diarrhea (2). Since its introduction into the United States, juices and food products containing mangosteen fruit have become a top-selling botanical supplement, with sales of beverages alone exceeding $200 million in 2008 (3). This commercial success has been largely the result of aggressive marketing of the putative health claims based on in vitro observations and anecdotal reports. In vitro activities include antibacterial (4–6), antioxidative (7,8), antiinflammatory (9–11), antiproliferative and proapoptotic (12,13), and antimetastatic (14,15) properties. Such activities have been most strongly associated with a unique family of compounds referred to as xanthones that are located in the pericarp of mangosteen (3,16). Xanthones in mangosteen fruit have a distinct C6-C1-C6 tricyclic ring system and often contain multiple hydroxy and isoprene ring systems (16). Xanthones in mangosteen pericarp, along with many other xanthones present in lower concentrations. Possible health-promoting activities of xanthones are also supported by several animal studies. For example, dietary administration of α-mangostin (0.05% by weight) significantly decreased development of aberrant crypt foci in 1,2-dimethylhydrazine–treated rats (17). Also, oral administration of 48 μmol α-mangostin/kg attenuated carrageenan-induced paw edema in mice (18).

The proposed health benefits of mangosteen rely on the assumption that the ingested compounds or their bioactive metabolites are delivered to target tissues. The bioavailability of mangosteen xanthones has received very limited attention. Kondo et al. (19) recently reported the presence of α-mangostin in plasma and male participants in mean pharmacokinetic values of α-mangostin in serum and urinary xanthones. Only 15.4 ± 0.7% of total xanthones in pericarp particles in the juice partitioned into mixed micelles during in vitro digestion. These results show that xanthones in mangosteen juice are absorbed when ingested along with a high-fat meal, although release of xanthones from pericarp particles during digestion may be limited. J. Nutr. 142: 675–680, 2012.

Abstract

The proposed health-promoting effects of the pericarp from mangosteen fruit have been attributed to a family of polyphenols referred to as xanthones. The purpose of this study was to determine the bioavailability of xanthones from 100% mangosteen juice in healthy adult participants (n = 10). Pericarp particles accounted for 1% of the mass and 99% of the xanthone concentration in the juice. The juice provided 5.3 ± 0.1 mmol/L total xanthones with α-mangostin, garcinones (C, D, and E), γ-mangostin, gartanins, and other identified xanthones accounting for 58, 2, 6, 4, and 5%, respectively. Participants ingested 60 mL mangosteen juice with a high-fat breakfast. Free and conjugated (glucuronidated/sulfated) xanthones were detected in serum and urine. There was marked variation in the AUC (762–4030 nmol/L × h), maximum concentration (113 ± 107 nmol/L), and time to maximum concentration (3.7 ± 2.4 h) for α-mangostin in sera during the 24-h collection. Similarly, xanthones in 24-h urine ranged from 0.9 to 11.1 μmol and accounted for 2.0 ± 0.3% (range 0.3–3.4%) of the ingested dose. There were no significant differences between female and male participants in mean pharmacokinetic values of α-mangostin in serum and urinary xanthones. Only 15.4 ± 0.7% of total xanthones in pericarp particles in the juice partitioned into mixed micelles during in vitro digestion. These results show that xanthones in mangosteen juice are absorbed when ingested along with a high-fat meal, although release of xanthones from pericarp particles during digestion may be limited. J. Nutr. 142: 675–680, 2012.

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3Supplemental Tables 1 and 2 and Supplemental Figures 1 and 2 are available from the “Online Supporting Material” link in the online posting of the article and from the same link in the online table of contents at http://jn.nutrition.org.
4This study was registered at clinicaltrials.gov as NCT01425047.
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the juice or xanthone metabolites in plasma. Li et al. (20) reported that rats absorbed only 0.4% of α-mangostin administered by gavage. Our primary objective in the present study was to determine the bioavailability of 7 of the more abundant xanthones present in mangosteen in healthy men and women who consumed a single dose of 100% mangosteen juice with a typical Western-style breakfast. The amounts of xanthones ingested, free and conjugated xanthones in urine, and α-mangostin in serum were investigated. Several of the other xanthones were detected in serum. Finally, to determine the level of bioaccessibility of the target compounds, mangosteen juice was subjected to simulated gastric and small intestinal digestion, and the amount of xanthones released from pericarp particles was measured.

Participants and Methods

Chemicals and reagents. All chemicals were purchased from Sigma Chemical Co. unless otherwise noted. HPLC-grade reagents were obtained from Fisher Scientific. α- and γ-Mangostins, garcinones D and E, and 8-deoxygartanin were purified (≥ 98% as assessed by NMR) as described elsewhere (21,22).

Mangosteen juice. Four commercial sources of “mangosteen juice” were initially purchased in local natural health stores to determine xanthone concentration. Three of these products that were marketed as mangosteen juice were actually blends containing other fruit juices. Total xanthone concentration in the products ranged from 0.48 ± 0.03 to 5.32 ± 0.19 mmol/L. The highest concentration of xanthones was present in the 100% mangosteen juice product used in this study. The juice product was a colloidal suspension containing both liquid and pericarp particles (pulp). The profile of xanthones in mangosteen juice is presented in Table 1. The dry weight of pericarp in juice was 10.6 ± 0.2 g/L, with particle sizes ranging from >74 to ≤149 μm. Juice was centrifuged (10,000 × g, 35 min at 4°C) to separate the liquid and pericarp particles to determine the xanthone concentration of each fraction and to assess extent of bioaccessibility using in vitro digestion (see below).

Participants. Informed consent was obtained from all participants, and the study procedures were approved by the OSU11 Biomedical Sciences Committee of the Institutional Review Board, Office of Responsible Research Practices. Nonsmoking, healthy adult participants (5 males and 5 females) were recruited by word of mouth among OSU students and staff. Study eligibility required participants to be non-smoking healthy adults with a BMI ≤30 kg/m2 and normal renal function. Exclusion criteria included pregnancy, acute and chronic diseases, a history of gastrointestinal tract pathology, and either weight loss of ≥10% or use of dietary supplements, herbs, or antibiotics during the 6-mo period preceding entry into the study.

Study design and sampling. Participants were required to refrain from consuming mangosteen fruit, mangosteen juice, and other mangosteen-containing foods and beverages for 1 wk before the study and to refrain from drinking wine the day before and day of the study. After an overnight fast (≥10 h), participants were admitted to the OSU CRC (0600–0700) for collection of baseline blood (0 h). Because the suggested serving of mangosteen juice products for proposed health-promoting activity on labels is 28-84 mL/d, participants received 60 mL of well-mixed mangosteen juice along with a typical fast-food (i.e., high-fat) breakfast consisting of English muffin (64 g), sausage (50 g), egg (65 g), and cheese (21 g) along with 6.8 g canola oil and 6.8 g soybean oil. Coffee (without creamer or fat-containing milk), tea, water, nonfat milk, or carbonated beverages were available. The total energy of the meal was 485 kcal, with protein, carbohydrate, and fat accounting for 23, 23, and 54%, respectively. The ratio of SFA : MUFA : PUFA was 2.1:1.6:1.0 (total fat = 28.1 g). This meal also contained 1.54 g dietary fiber. Subjects ingested the meal within 10 min and remained in the CRC for collection of blood at 1, 2, 3, 4, 6, and 8 h. After the 4-h collection of blood, participants consumed lunch consisting of white bread (50 g), butter (5 g), cheese (28.4 g), salad dressing (14.7 g), turkey breast (90 g), chicken noodle soup (126 g), crackers (6 g), pudding, (99 g) and the same selection of beverages as for the breakfast. Free access to water and coffee was provided throughout the day; a single participant drank a single cup of coffee after meals until release from the CRC. An optional snack of pretzels (28.4 g) and low-fat yogurt (245 g) was provided at 1500. Upon release from the CRC, participants were advised that there were no dietary restrictions for dinner other than to refrain from products containing mangosteen fruit or mangosteen-containing fruit spread, gelatin, wine, or carbonated beverages. Participants completed a dietary record of all ingested food and beverages, and analysis indicated complete compliance by all study participants.

A pretest sample of urine (baseline) was collected upon arrival at the CRC. Urine was also collected during the stay at the CRC (0–8 h) and continuously from 8 to 24 h by participants after release from the CRC. The total volume of urine for the 0–8-h and 8–24-h collections was measured, and an aliquot was stored at −20°C for analysis of xanthones within 2 wk.

Estimated bioaccessibility of xanthones in mangosteen juice during in vitro digestion. Intact mangosteen juice (2 mL), the liquid fraction of the juice (2 mL), and pericarp particles from 2 mL intact mangosteen juice were separately mixed with 2.0 g nonfat yogurt containing 0–3% soybean oil to assess bioaccessibility. Samples were subjected to simulated gastric and small intestinal digestion as described in detail elsewhere (23). The recovery of xanthones after simulated digestion was >70%, except for 8-deoxygartanin, which was 61%. The quantity of xanthones partitioning in the aqueous fraction of chyme after completion of simulated small intestinal digestion is referred to as being bioaccessible, i.e., having the potential to be absorbed.

Extraction and analysis of xanthones. Aliquots of serum and urine were incubated with or without a glucuronidase/sulfatase enzyme mixture from Helix pomatia (9626; Sigma Chemical Co.) for 2 h at 37°C to hydrolyze xanthone conjugates, followed by solid-phase extraction using C18 cartridges (24). Mangosteen juice, the separated liquid and pericarp (“pulp”) fractions of juice, and the chyme and aqueous fraction after in vitro digestion were extracted into ethyl acetate for analysis. The HPLC system and chromatographic separation of xanthones have been described elsewhere (21). Garcinones D and E, α- and γ-mangostins, and 8-deoxygartanin were identified by comparison of time to elution and spectrum with standards (≥98% purity as determined by 1H- and 13C-NMR) (4). Concentrations were determined by comparison with known quantities of pure compounds that were prepared gravimetrically. The 5-point calibration curves were linear with a correlation coefficient >0.998, and the lower limit of detection of xanthones was 12.2 nmol/L (signal to noise ratio = 3). Because standards for garcinoine C, garatin, 6-dihydroxy-methoxy-dimethyl- pyranone, and tovophillin B were not available, each of these compounds was identified by comparison of time to elution and UV spectrum with values in the literature (21,22). Concentrations were estimated as equivalents of garcinoine D for garcinoine C, 8-deoxygartanin for garatin, and α-mangostin for 6-dihydroxy-methoxy-dimethyl-pyranone and tovophillin B.

Because the method described above lacked sufficient sensitivity to detect xanthones other than α-mangostin in serum, several samples containing the highest concentration of α-mangostin were selected for analysis by HPLC-MS to determine if other xanthones were present. A more rapid HPLC method was developed with the Synergi analytical column (4 μm, 4.6 × 150 mm; Phenomenex). The mobile phase did not include acid because the signal improved several-fold using water and acetonitrile. The gradient was as follows: 40% to 95% acetonitrile over 3 min followed by a 6 min reequilibration with 40% acetonitrile. An Alliance 2695 HPLC system was utilized with a flow rate of 1.3 mL/min and a column temperature at 35°C. Xanthone identities and elution order were confirmed by comparison with the longer run HPLC method (described above) using pure standards. The HPLC eluate

11 Abbreviations used: Cmax, maximum serum concentration; CRC, Clinical Research Center; OSU, Ohio State University; Tmax, time to the maximum serum concentration.

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Differences at simulated digestion of mangosteen juice was analyzed by 1-factor of individual xanthones into the aqueous fraction of chyme during xanthones in urine. The impact of the amount of fat on the partitioning t-test was used to compare within-group changes over time for and urinary xanthones for female and male participants. Welch paired characteristics, pharmacokinetic parameters for used to assess whether there were significant differences between general participants and Methods.

Miscellaneous analyses. Urinary creatinine was analyzed by HPLC according to Achari et al. (25). Serum cholesterol was analyzed by enzymatic colorimetric method using the CHOL2 COBAS assay kit according to the manufacturer’s instructions (Roche Diagnostics).

Analysis of serum α-mangostin data. Postprandial absorption of α-mangostin in serum was expressed as baseline-corrected AUC during the 24-h period after ingesting breakfast with mangosteen juice by trapezoidal approximation using Igor Pro 4.0 software (Wave Metrics). The Tmax and 24-h period after ingesting breakfast with mangosteen juice by trapezoidal approximation using Igor Pro 4.0 software (Wave Metrics). The Tmax and were estimated by the product of concentration of total xanthones (free + conjugated) in urine and total urine volume.

Statistical analysis. A Welch unpaired t test (GraphPad Software) was used to assess whether there were significant differences between general characteristics, pharmacokinetic parameters for α-mangostin in serum, and urinary xanthones for female and male participants. Welch paired t-test was used to compare within-group changes over time for xanthones in urine. The impact of the amount of fat on the partitioning of individual xanthones into the aqueous fraction of chyme during simulated digestion of mangosteen juice was analyzed by 1-factor ANOVA followed by Tukey’s honestly significant difference test (SPSS). Differences at P < 0.05 were considered significant. Values shown in the text are means ± SD.

Results

All 10 participants completed the study, and none reported gastrointestinal distress after consuming the test sample of 60 mL mangosteen juice. BMI was within the healthy range for all participants. Serum cholesterol and urinary creatinine were normal in healthy adults (26). These variables and age did not differ between female and male participants (Supplemental Table 1).

Xanthones in serum. α-Mangostin was the only xanthone detected in serum by HPLC-Diode-Array Detector, indicating that the concentration of other xanthones was <12.2 nmol/L. The AUC, Cmax, and Tmax of serum α-mangostin were similar in female and male participants (Table 2). The serum concentration of α-mangostin increased rapidly after ingestion of the mangosteen juice with the breakfast meal (Fig. 1) One participant (no. 3) had a markedly greater AUC (4030 nmol/L × h) and Cmax (450 nmol/L) compared with all other participants. After a steep decline, the concentration of α-mangostin in the serum of participants 1, 3, 7, and 8 increased again at 6–8 h, although the maxima of the second peaks were less than those of the respective initial peaks. These data suggested one or more of the following possibilities: the xanthone-free meal at lunch stimulated absorption of the xanthones retained in enterocytes or enhanced lymphatic flow into circulation, xanthones were reabsorbed by enterohepatic circulation, or xanthones also may be absorbed in the large intestine. Serum α-mangostin did not differ significantly between 8 h (71 ± 87 nmol/L) and 24 h (33 ± 18 nmol/L). The Cmax of total α-mangostin ranged from 42 to 450 nmol/L, and the Tmax for total α-mangostin was 2–4 h in 8 of the participants, and 8 h for the 2 remaining participants (Table 2).

<table>
<thead>
<tr>
<th>Xanthones</th>
<th>Juice Cmax (μmol/L)</th>
<th>Percentage of total xanthones identified</th>
<th>Liquid portion</th>
<th>Pericarp Distribution in juice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garcinone C</td>
<td>291 ± 11.2</td>
<td>5.5%</td>
<td>5.5 ± 0.2</td>
<td>263 ± 15.3</td>
</tr>
<tr>
<td>Garcinone D&lt;sup&gt;2&lt;/sup&gt;</td>
<td>520 ± 10.9</td>
<td>10.2%</td>
<td>5.8 ± 0.3</td>
<td>465 ± 23.5</td>
</tr>
<tr>
<td>Garcinone E&lt;sup&gt;2&lt;/sup&gt;</td>
<td>239 ± 18.5</td>
<td>5.1%</td>
<td>1.7 ± 0.2</td>
<td>214 ± 6.9</td>
</tr>
<tr>
<td>α-Mangostin&lt;sup&gt;2&lt;/sup&gt;</td>
<td>3190 ± 123</td>
<td>59.9%</td>
<td>12.2 ± 0.5</td>
<td>3100 ± 195</td>
</tr>
<tr>
<td>β-Mangostin</td>
<td>121 ± 9.3</td>
<td>2.3%</td>
<td>0.9 ± 0.1</td>
<td>111 ± 3.3</td>
</tr>
<tr>
<td>γ-Mangostin&lt;sup&gt;2&lt;/sup&gt;</td>
<td>356 ± 4.3</td>
<td>6.5%</td>
<td>1.9 ± 0.2</td>
<td>326 ± 4.5</td>
</tr>
<tr>
<td>8-Deoxygartanin&lt;sup&gt;2&lt;/sup&gt;</td>
<td>176 ± 4.5</td>
<td>3.1%</td>
<td>2.4 ± 0.0</td>
<td>155 ± 5.0</td>
</tr>
<tr>
<td>Gartanin</td>
<td>157 ± 6.9</td>
<td>2.8%</td>
<td>2.7 ± 0.2</td>
<td>149 ± 3.4</td>
</tr>
<tr>
<td>Tovophillin B</td>
<td>50 ± 2.9</td>
<td>1.1%</td>
<td>ND</td>
<td>48 ± 0.7</td>
</tr>
<tr>
<td>1,8-Dihydroxy-methoxy-dimethyl-pyranone</td>
<td>193 ± 7.4</td>
<td>3.6%</td>
<td>ND</td>
<td>175 ± 10.9</td>
</tr>
<tr>
<td>Total</td>
<td>5290 ± 166</td>
<td>100%</td>
<td>33.0 ± 0.5</td>
<td>5000 ± 200</td>
</tr>
</tbody>
</table>

<sup>1</sup> Values are means ± SD; n = 5 independent replicates.
<sup>2</sup> Standards (>98% pure) available in our laboratory. Concentrations of garcinone C and gartanin were estimated as equivalents of garcinone D and 8-deoxygartanin, respectively, and 6-dihydroxy-methoxy-dimethyl-pyranone and tovophillin B were estimated as equivalents of α-mangostin as described in Participants and Methods.

Males

<table>
<thead>
<tr>
<th>Participant</th>
<th>AUC (nmol/L × h)</th>
<th>Cmax (nmol/L)</th>
<th>Tmax (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>1004</td>
<td>42</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td>771</td>
<td>44</td>
<td>8</td>
</tr>
<tr>
<td>8</td>
<td>1798</td>
<td>154</td>
<td>4</td>
</tr>
<tr>
<td>9</td>
<td>816</td>
<td>42</td>
<td>2</td>
</tr>
<tr>
<td>10</td>
<td>762</td>
<td>49</td>
<td>2</td>
</tr>
</tbody>
</table>

Females

<table>
<thead>
<tr>
<th>Participant</th>
<th>AUC (nmol/L × h)</th>
<th>Cmax (nmol/L)</th>
<th>Tmax (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>1870 ± 1230</td>
<td>159 ± 165</td>
<td>3.8 ± 2.4</td>
</tr>
</tbody>
</table>

<sup>1</sup> Cmax, maximum serum concentration; Tmax, time to the maximum serum concentration.
The mean ratio of free to conjugated α-mangostin in serum was ~2.7:1.0 (73.0 ± 3.7% vs. 27.0 ± 3.7%) from 1–8 h and 2.8:1.0 (73.5 ± 23.4% vs. 26.5 ± 23.4%) at 24 h. However, there was considerable interindividual variation in the extent to which serum α-mangostin was conjugated during the collection period. The ranges of conjugated α-mangostin in serum among participants were 9–48%, 6–49%, 4–35%, 3–70%, 4–42%, <1–79%, and <1–73% at 1, 2, 3, 4, 6, 8, and 24 h, respectively. Serum from 3 participants collected at $C_{\text{max}}$ was analyzed by HPLC-MS to provide additional sensitivity to identify xanthones other than α-mangostin. Preliminary HPLC-accurate mass data indicated the presence of garcinone D, α-mangostin, 8-deoxygartanin, and garcinan in serum (Supplemental Fig. 1). γ-Mangostin, garcinone E, and tovophillin B also were detected in serum from 1 of the 3 participants (no. 3). Double peaks were observed for garcinone D (peaks 1a and 1b) and 8-deoxygartanin (peaks 2a and 2b) (Supplemental Fig. 1) in serum from all participants. These likely were cyclized isomers of the parent compounds because they exhibited the same accurate mass and similar retention behavior. Standards, as well as pericarp extracts, also displayed these minor forms.

**Xanthones in urine.** Xanthones were not detected in the urine of participants at baseline. Both free and conjugated xanthones were present in urine of all participants after ingestion of the mangosteen juice (Table 3). The relative quantities of the different xanthones in urine were similar to those in mangosteen juice with the exception of the absence of garcinone C (data not shown). The amount of total xanthones in urine during the 24-h collection period represented 2.0 ± 0.3% of the ingested dose and did not differ between males and females. The rate of xanthone excretion during the 0–8-h collection period (342 ± 49 nmol/h) was greater than between the 8- and 24-h collection period (205 ± 20 nmol/h) ($P < 0.01$).

There was marked interindividual variability in the relative amounts of free and conjugated species of each xanthone excreted during the 24-h collection period (Table 3). For example, the percentages of total garcinone D and α-mangostin in urine that were conjugated ranged from 2 to 80% and from 9 to 54%, respectively (data not shown). The extent of conjugation of the various xanthones in urine from a participant was similar and independent of gender (data not shown).

**Bioaccessibility of xanthones from mangosteen juice during in vitro digestion.** Partitioning of xanthones into the aqueous or bioaccessible fraction of chyme generated during simulated digestion of mangosteen juice increased in proportion to the amount of soybean oil added to the mixture of mangosteen juice and yogurt ($P < 0.001$) (Supplemental Fig. 2). In the absence of oil, 8–15% of the xanthones were present in the aqueous fraction of chyme. This increased to 27–33% during digestion of the juice and yogurt mixture containing 3% soybean oil. There were <1% of xanthones partitioned in the aqueous fraction of chyme when the bile extract was omitted during digestion of the juice containing 3% soybean oil (data not shown), suggesting that the bioaccessibility of xanthones was partially dependent on their incorporation into mixed micelles. Partitioning of xanthones from the separated liquid and pericarp fractions of mangosteen juice into the bioaccessible fraction of chyme during simulated digestion was also compared. The quantity of xanthones released from the pericarp into the aqueous fraction of chyme greatly exceeded that from the liquid fraction because the pericarp contained 99% of the xanthones in the juice (Supplemental Table 2). In contrast, the efficiency of partitioning of xanthones in the aqueous fraction of juice (liquid part) in the aqueous fraction of chyme (84.7 ± 1.4%) greatly exceeded that during the digestion of pericarp (15.4 ± 0.7%) ($P < 0.001$).

**TABLE 3** Excretion (24 h) of xanthones into urine accounts for ~2% of the dose of mangosteen juice ingested by female and male participants

<table>
<thead>
<tr>
<th>Participants</th>
<th>Urinary xanthones</th>
<th>nmol/24 h</th>
<th>Free:conjugated</th>
<th>nmol/mg Creatinine</th>
<th>Apparent absorption %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>8380</td>
<td>40:60</td>
<td>18.5</td>
<td>2.6</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>5384</td>
<td>49:51</td>
<td>10.5</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>11,151</td>
<td>38:62</td>
<td>8.3</td>
<td>3.4</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>4932</td>
<td>52:48</td>
<td>4.4</td>
<td>10.5</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>8988</td>
<td>65:35</td>
<td>2.9</td>
<td>0.3</td>
<td></td>
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<tr>
<td>Mean ± SD</td>
<td>5670 ± 3560</td>
<td>58 ± 16.74</td>
<td>15.7</td>
<td>8.9 ± 7.5</td>
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Discussion

This is the first study to our knowledge to examine the bioavailability of multiple xanthones in human participants after consumption of mangosteen juice as part of a meal. Both free and glucuronidated/sulfated conjugates of the most abundant xanthones in mangosteen juice were present in serum and urine. The relative amounts of the individual xanthones in urine were similar to those in the juice, suggesting that the apparent absorption of these compounds was minimally affected by their structural differences. Absorption from this juice product was estimated to be 2% of the ingested dose as assessed by the quantity of total xanthones in urine collected for 24 h. The concentration of α-mangostin in serum and the total quantity of xanthones in urine varied ~10-fold among participants. Results from simulated gastric and small intestinal digestion of mangosteen juice suggested that the apparently low bioavailability was primarily due to inefficient release of xanthones from pericarp particles. Transformation of ingested xanthones to bioactive metabolites by gut bacteria and human cells (27), secretion of xanthines into bile, and retention in tissues beyond the 24-h collection period may underestimate the extent of absorption based solely on 24-h urinary content.

Kondo et al. (19) previously reported the presence of α-mangostin in serum from human participants who ingested 59 mL of a blended juice containing mangosteen, aloe vera, green tea, and multivitamins before breakfast. “Mangostin” (not defined) concentration was 3.8 mmol/L and the Cmax for α-mangostin in plasma was 7.6 ± 3.7 mmol/L. The Tmax was 1 h, and the xanthone was detected for ≤6 h postingestion. The quantities of mangostins (α, β, and γ-mangostin) and total xanthones in mangosteen juice in the present study were 3.7 and 5.3 mmol/L, respectively (Table 1). Apparent absorption was greater in our study with the Cmax for α-mangostin increased by 5-fold. Differences that accounted for the greater absorption of α-mangostin in our study include determination of both free and conjugated α-mangostin and co-consumption of the juice with a breakfast meal containing a high amount of fat. We previously reported that α-mangostin was partially conjugated by Caco-2 human intestinal cells and that free and conjugated compounds effluxed across the basolateral membrane (28). A prandial-like state in Caco-2 cell cultures, i.e., presence of oleate: taurolcholate micelles in the apical compartment, stimulated transepithelial flux of free, but not conjugated, α-mangostin, suggesting that the free compound was incorporated into chylomicrons and secreted. For this reason, mangosteen juice and a high-fat breakfast were consumed together in the present study to increase partitioning of xanthones into mixed micelles for delivery to enterocytes and subsequent secretion into lymph. The Tmax of 3.7 h in the present study compared with the Tmax of 1 h reported by Kondo et al. (19) is likely due to slower gastric emptying when the juice was consumed with the high-fat meal. Finally, it is possible that compounds in tea and aloe vera present in the juice blend ingested by participants in the previous study (19) may have attenuated the bioaccessibility and absorption of xanthones.

Li et al. (20) recently reported the first pharmacokinetic investigation of α-mangostin. Rats were administered pure α-mangostin solubilized in 2% ethanol and Tween 80 for intravenous and oral delivery, respectively. The pharmacokinetic profile of intravenously administered α-mangostin included a rapid tissue distribution phase and a slow elimination phase. However, the oral bioavailability of α-mangostin from a 20-mg dose without a meal was extremely low (~0.4%). We have found both free and phase 2 metabolites of xanthones in tissues of mice chronically fed an AIN-93G diet containing 5% fat and 0.1% (wt/wt) α-mangostin, confirming the absorption and metabolism of dietary xanthones (29).

Whole juice and its aqueous and pericarp components were separately subjected to simulated gastric and small intestinal digestion to provide insight on the apparent poor bioavailability of xanthones in the participants. Only 15% of the xanthones in this juice product partitioned in the bioaccessible fraction of chyme. Because 99% of the xanthones were in pericarp, the release of xanthones from undigested material appears to be the limiting factor for xanthone bioaccessibility from the juice. Bioavailability of dietary compounds is affected by numerous factors including size of ingested food particles (e.g., 30) because increased surface area increases the access of digestive enzymes. Materials that are not digested in the upper gut pass to the large intestine where fermentation of the matrix may release compounds that can be transformed to bioactive compounds by the microbiota. The fate of pericarp xanthones in the large intestine and innovative strategies to enhance release of xanthones from the pericarp during preparation of juice products merit investigation.

The profile of the individual xanthones in urine was similar to that in mangosteen juice, suggesting that there may be limited impact of xanthone structure on absorption and excretion. In contrast, there were marked variations in the concentration of α-mangostin in serum, the amounts of xanthones in urine, and the ratio of free to conjugated metabolites of xanthones in serum and urine among participants consuming the same quantity of mangosteen juice. Heterogeneity in serum concentrations of dietary phytochemicals is common, and the genetic and physiologic basis of such differences are only beginning to be understood. For example, polymorphisms in xenobiotic metabolizing enzymes and transporters are known to influence the absorption and biotransformation of drugs and phytochemical compounds (31,32).

The presence of free α-mangostin and other xanthones in serum is particularly interesting because concentrations of ≤10 μmol/L exhibit antiinflammatory, antiproliferative, and proapoptotic effects in vitro (9–12). The question is whether concentrations of xanthones in body fluids and tissues are sufficient to mediate the proposed health-promoting activities in humans. Cmax for α-mangostin in this study in participants consuming 60 mL of 100% mangosteen juice were submicromolar. Chronic consumption of ≤500 mL mangosteen juice for 8 wk was not associated with reported side effects or significant changes in vital signs (33), suggesting that tissue concentrations of xanthones may approach those shown to mediate phenotypic changes in cellular studies. It is interesting that reduced C-reactive protein and other antiinflammatory markers in serum have been recently reported for 2 randomized, double-blinded, placebo-controlled studies in healthy participants consuming a mangosteen juice blend daily for 4 and 8 wk (33,34). Because the blend used in these trials contained numerous components in addition to mangosteen juice, it is unclear if the observed antiinflammatory activity was mediated by xanthones. Further investigation using pure mangosteen juice will facilitate evaluation of proposed health-promoting activities of xanthones in vivo.

The results from this study clearly show that xanthones are absorbed and can be transformed to phase 2 metabolites. The relative bioactivities of the ingested xanthones and their metabolites in humans merit investigation. The above data provide a foundation for the design of future investigations to further elucidate the absorption, metabolism, and potential efficacy of dietary xanthones.

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in the design and conduct of the trial. C.C., S.K.C. and M.L.F. conceived and designed the research plan and provided oversight; C.C. and K.M.R. conducted the research and analyzed the data; S.S. and A.D.K. provided the pure xanthone standards; M.L.F. and C.C. wrote the initial draft of the manuscript; and M.L.F. had primary responsibility for final content. All authors read and approved the final manuscript.

**Literature Cited**


