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Research Article

Bioaccessibility, biotransformation, and transport of α-mangostin from *Garcinia mangostana* (Mangosteen) using simulated digestion and Caco-2 human intestinal cells

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α- and γ-Mangostin are the most abundant prenylated xanthones present in the fruit of the mangosteen tree. These compounds have been reported to possess numerous bioactivities that have provided the impetus for use of mangosteen products as nutraceuticals and in functional foods and dietary supplements. The health-promoting benefits of mangosteen are dependent on delivery of the xanthones to target tissues. Here, we used simulated digestion and Caco-2 cells to investigate the digestive stability, bioaccessibility, and intestinal cell transport of α- and γ- mangostin. Recovery of α- and γ-mangostin after simulated digestion of pericarp and fruit pulp exceeded 90%. Transfer of α- and γ-mangostin to the aqueous fraction during simulated digestion was efficient (65 – 74%) and dependent on bile salts suggesting that micellarization is required for optimal bioaccessibility of xanthones. Cell uptake of xanthones from micelles was dose dependent and intracellular concentrations were maximum by 1 h. Both free and phase II metabolites of α-mangostin were transported in the basolateral compartment and metabolites also effluxed into the apical chamber. Transepithelial transport of α-mangostin was increased during prandial-like compared to fasted conditions suggesting that absorption is enhanced by dietary fat.

Keywords: Bioaccessibility / Caco-2 human intestinal cells / *In vitro* digestion / Mangosteen / Xanthones

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1 Introduction

Garcinia mangostana L. (mangosteen) is tropical fruit native to southeast Asia that is commonly referred as "the queen of fruits" [1]. Mangosteen has dark purple to red – purple exterior with an edible soft white pulp that is characterized by a sweet, slightly acidic flavor [2]. The tree can attain a height of 25 m with fruits 6 – 7 cm in diameter that contain 5 – 7 flattened seeds surrounded by a white pulp. The pericarp of mangosteen has been used in traditional Thai medicine for the treatment of skin infections, wounds, and diarrhea [3]. Recently, products containing mangosteen have become one of the top-selling botanical dietary supplements in the US, representing the sixth ranked single-herb dietary supplement with sales exceeding $120 million in 2005 [4].

The pericarp of mangosteen has been reported to contain the major prenylated xanthones, α- and γ-mangostin (Fig. 1), as well as several less abundant xanthones and related compounds [5]. Xanthones contain a distinctive tricyclic aromatic ring system. These xanthones exhibit antimicrobial [6], antiretroviral [7], antimalarial [8], anticarcinogenic [1, 9, 10] antioxidative [2, 11], anti-inflammatory [12 – 14], and neuroprotective [15] activities *in vitro*. Also, antilipidemic [16] and cardioprotective [17] activities have been reported in animal studies. Collectively, these reported activities have provided the impetus for the use of mangos-

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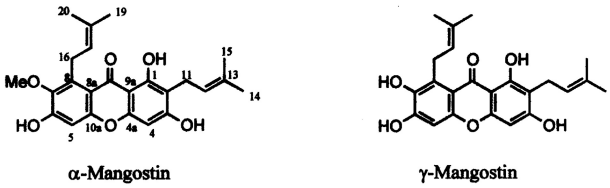

Figure 1. Structures of α- and γ-mangostin.

teen products as nutraceuticals and incorporation into functional foods and dietary supplements [2].

The health-promoting effects of mangosteen requires delivery of bioactive xanthones to target tissues. At present, there are no data regarding the bioavailability of the major xanthones from mangosteen. The objective of the study described below was to examine the digestive stability, bioaccessibility, uptake, and transport of α- and γ-mangostin from the pericarp and fruit pulp of mangosteen using the coupled simulated digestion and Caco-2 human intestinal cell model.

2 Materials and methods

2.1 Chemicals and standards

Unless indicated otherwise, all chemicals and reagents were purchased from Sigma Chemical (St. Louis, MO), Gibco (Invitrogen, CA), Fisher Scientific (Fair Lawn, NJ), and Pierce Biotechnology, (Rockford, IL). α-Mangostin and γ-mangostin were purified as described previously [18]. Briefly, the fruit of *G. mangostana* was collected from the family orchards of one of the investigators (AB) that is located in the Kombang district, Chanthaburi province, Thailand. Pericarp (0.5 kg) was air-dried and powdered before extraction with ethyl acetate at 50°C for 48 h and the solvent was evaporated to yield crude extract. Xanthones were separated by repetitive column chromatography (silica gel $60GF_{254}$) using various solvents. Purity of α- and γ-mangostin exceeded 98 and 95%, respectively, as determined by HP-FAB-MS. Structural identity was confirmed by 1D and 2-D NMR. α-Mangostin (purity > 95%) also was received as a gift from Dr. Thomas Tritt, Renaissance Herbs, CA, for use as a standard.

2.2 Preparation of sample for simulated digestion

Fresh *G. mangostana* (mangosteen) were obtained from the family garden of one of the investigators (AB) in Chanthaburi, Thailand. Fruits were washed, dried, and separated into pericarp or fruit pulp. Fruit pulp was directly blended and pureed. Deionized water (0.7 mL/ g) was added before preparing puree of pericarp. Aliquots were transferred to 50 mL sealed tubes under a stream of nitrogen and stored at –80°C.

2.3 *In vitro* digestion

Simulated digestion reactions (50 mL total volume) contained either 352 mg pericarp or 600 mg fruit pulp of mangosteen and 200 μL soybean oil, as mangosteen fruit is usually consumed as part of meal and soybean oil is widely used in cooking. Details for simulating the gastric and small intestinal phases of digestion were similar to that described previously [19]. Modifications of the original procedure included the following: acidification of samples to pH 3.0 ± 0.1 instead of pH 2.0 as the presence of food temporarily increases pH in gastric lumen [20]; addition of porcine lipase (0.2 mg/mL) along with porcine pancreatin (0.4 mg/mL) and bile extract (2.4 mg/mL) to facilitate efficient hydrolysis of triglycerides and micellarization of lipophilic products of digestion [21]; and, centrifugation of digesta at 3000 × *g* for 90 min at room temperature for isolation of aqueous fraction (Beckman Model GS-6, Fullerton, CA) instead of centrifugation at 167 000 × *g* for 40 min as the reduced force does not significantly affect isolation of compounds partitioned into mixed micelles [22]. Examination of the role of bile salts in the partitioning of xanthones in the filtered (0.22 μm) aqueous fraction was addressed by omitting bile extract during the small intestinal phase of simulated digestion for one set of samples. Aliquots of digesta and filtered aqueous fraction were blanketed with nitrogen gas and stored at –80°C until analysis. Recovery of the xanthones in pericarp and pulp after simulated digestion was calculated by dividing the amounts of α- and γ-mangostin in digesta by that present in the predigested sample. The amounts of these xanthones present in the filtered aqueous fraction after small intestinal digestion is referred to as the bioaccessible fraction, *i.e.*, available for uptake by absorptive epithelial cells.

2.4 Cytotoxicity test of α and γ-mangosteen

Sulforhodamine B assay kit (Sigma TOX-6) was used to assess the possible cytoxicity of magostin. Monolayers of Caco-2 cells (11 days postconfluency) were exposed to either α- or γ-mangostin at concentrations ranging from 0–200 μmol/L. Test media were removed after 4 h and monolayers were washed once with sterile warm PBS before initiating the SRB assay according to the protocol provided by the manufacturer. Absorbance at 592 and 690 nm for cultures exposed to all concentrations of the mangostins was not significantly different from control cultures.

2.5 Uptake and retention of xanthones by Caco-2 human intestinal cells

Caco-2 cells (HTB37, American Type Culture Collection; passages 26–34) were maintained as previously described [19, 21]. For initial experiments examining the uptake of the xanthones, cells directly attached to plastic wells were used 11–14 day after monolayers became confluent as the

brush border membrane is fully differentiated at this time [23]. Monolayers were washed once with DMEM (37°C) before incubation for 4 h at 37°C in humidified atmosphere of 95% air/5% CO_2 in medium containing diluted filtered aqueous fraction (6.25 – 25% total vol.) generated during simulated digestion. To examine intracellular retention of xanthones, cultures exposed for 4 h to medium containing xanthones were washed once with PBS containing albumin (2 g/L) before adding fresh DMEM without xanthones and incubating for an additional 1 – 16 h. Medium and cells were collected and analyzed by HPLC. Cellular protein concentrations were determined by the bicinchoninic acid (BCA) method (Pierce).

2.6 Transport and metabolism of α-mangostin by Caco-2 cells

To characterize transepithelial transport from apical compartment to the basolateral compartment, cells were cultured on Transwell inserts (24 mm diameter, 0.4 μm pore size) until 21 – 25 day postconfluency as previously described [21]. Lipoprotein synthesis and secretion by Caco-2 cells are maximal 3 -wk after the monolayer reaches confluency [24]. After washing the monolayers as above, 2 mL DMEM containing 1.0 mM sodium oleate, 0.5 mM taurocholate, 0.5 mM phenol red, and Tween 40 micelles with 20 μmol/L α- mangostin were added to the apical compartment. The oleate – taurocholate (1.0:0.5 mM) micelles were added to simulate prandial conditions and thus stimulate chylomicron assembly and secretion [25]. Preliminary studies showed that this medium was not cytotoxic. Phenol red-free DMEM plus 1% FBS was added to the basolateral compartment. Cultures were incubated (37°C, 5% CO_2) for 0.5 – 6 h. Apical and basolateral media were collected at indicated times and the monolayer was washed, scrapped into ice-cold PBS, and collected by centrifugation to characterize the distribution and speciation (free *vs*. conjugated) of α-mangostin in the three compartments. In a separate experiment, oleate and taurocholate were deleted from apical medium to compare transport under fasting-like conditions with the prandial state. In another experiment, the flux of α-mangostin from basolateral to the apical compartment was examined. DMEM containing 10 and 0 μmol/L α-mangostin was added to the basolateral and apical compartments, respectively. α-Mangostin equivalents (free and conjugated) in apical and basolateral media and cells were determined after 3 h incubation.

Diffusion of phenol red across the monolayer from apical to the basolateral chamber was used as an indicator of monolayer integrity [21]. Monolayer integrity was not affected by exposure to α-mangostin as the hourly rate of flux of phenol red from the apical to the basolateral compartment was 0.009 ± 0.002%/cm^2 and 0.011 ± 0.003%/cm^2 ($p > 0.05$) for monolayers incubated in control medium and medium containing α-mangostin for 4 h.

2.7 Extraction and HPLC analysis of xanthones

Thawed samples of homogenized food, digesta, aqueous fraction, and medium from apical and basolateral compartments were extracted by adding 1.5 volume of ethyl acetate [18], mixing for 1 min, and centrifugation (2000 × *g*, 5 min). Additional extractions did not significantly increase recovery. α-Tocopherol acetate (1.0 – 1.5 μmol/L) was added as internal standard and 96 ± 1% was recovered with single extraction. An aliquot of the supernatant was then transferred to a glass vial, dried under nitrogen at room temperature, and resolubilized in ACN. The mixture was vortexed and filtered (0.2 mm syringe filter) prior to HPLC analysis. Frozen pellets of Caco-2 cells collected in experiments examining uptake and transport of xanthones were thawed before the addition of 10 g/L porcine protease in PBS. After incubation in a shaking water bath (37°C, 65 rpm, 30 min), the mixture was sonicated for 10 s on ice. Then, SDS (34.6 mmol/L) in ethanol (1.0 mL) was added before mixing for 1 min. Xanthones were extracted in ethyl acetate as above.

To determine the presence of phase II conjugates of α-mangostin, replicate samples of apical and basolateral medium, as well as sonicated cell pellets, were incubated with β-glucuronidase (500 units/mL) from *Helix pomatia* in 0.5 mL sodium acetate buffer (0.2 mol/L, pH 5) with shaking at 65 rpm (Varimax M48725, Thermolyne, Dubuque, IA) for 18 – 20 h at 37°C before extraction as above. Amount of conjugated α-mangostin was calculated by subtracting the amount of free α-mangostin in samples that were not treated with β-glucuronidase from the amount of α-mangostin equivalents in samples treated with enzyme.

Xanthone concentrations for all samples were determined by HPLC using Hewlett Packard Model 1100 (mangosteen analysis and bioaccessibility studies) and Waters 2695 (transport and biotransformation studies) separation models with photodiode array detectors. An analytical Synergi RP column (150 mm × 4.60 mm, 4 mm, (Phenomenex, CA), was used and protected by silica guard column (4.6 mm id × 50 mm). Column temperature was held constant at 35°C to control for temperature fluctuations in the laboratory at different times. Xanthones were separated using a mobile phase consisting of ACN (solvent A) and 2.0% acetic acid in water (v/v; solvent B), with the following solvent gradient at a flow rate of 0.8 mL/min: 0 – 5 min, 30% A; 5 – 15 min, 80% A; 15 – 25 min, 30% A. Xanthones were detected at 254 nm and their identification was confirmed by retention time and spectral analysis with quantity measured against the standard curve generated from pure standards. Recovery after extraction and analysis exceeded 97 ± 5% as determined by monitoring concentration of exogenous α-tocopherol acetate at 292 nm in eluent. The LOD for α- and γ-mangostin were ≥97 and ≥101 nmol/L, respectively. Within day coefficients of variation (CV) for extraction and analysis of replicate aliquots of the same

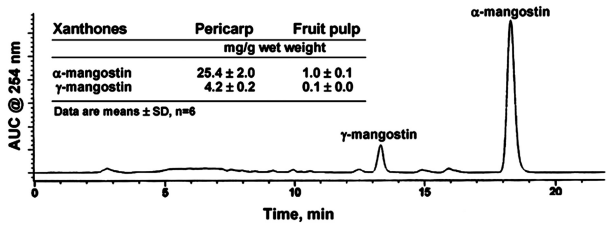

Figure 2. Representative HPLC chromatogram of xanthones extracted from mangosteen. Concentrations of α- and γ-mangostin in pericarp and fruit pulp are indicated in the tabular insert. Data are means ± SD; $n = 6$.

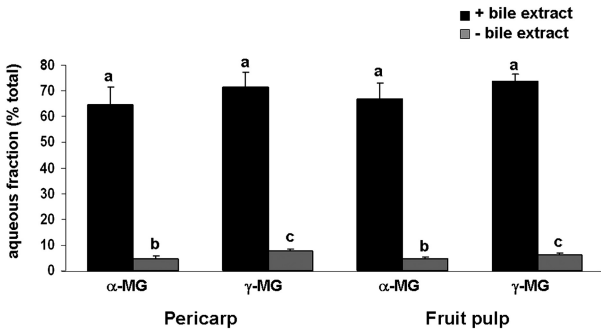

Figure 3. Efficient transfer of α- and γ-mangostin from pericarp and fruit pulp to aqueous fraction during simulated digestion requires bile extract. Bile extract was either present or absent during small intestinal phase of digestion. Efficiency represents the percentage of the xanthones in mangosteen tissue transferred to the filtered aqueous fraction during simulated digestion. Data are means ± SD; $n = 6$. Means without a common letter above error bar differ significantly ($p < 0.05$).

samples were 1.9 and 2.1% for α- and γ-mangostin, respectively. The interday CV for replicates of the same samples were similar (1.5 and 1.9% for α- and γ-mangostin, respectively).

2.8 Statistical analysis

SPSS version 16 for windows was used for all statistical analyses. All tests were conducted in triplicate and each experiment was repeated at least once to provide a minimum of six independent observations. Descriptive statistics including mean and SD were calculated for digestive stability, the efficiency of micellarization, the stability of micellarized xanthones in cell culture medium, the uptake, retention, and transport of xanthones by Caco-2 cells. Means were compared using one-way ANOVA followed by Tukey's *post hoc* test or paired *t*-test. Differences were considered significant at $p < 0.05$.

3 Results

3.1 Quantity of major xanthones in mangosteen fruit

α- and γ- mangostin were present in both pericarp and fruit pulp. Representative HPLC chromatogram of extracts of mangosteen is presented in Fig. 2. The concentration of these xanthones in pericarp and fruit pulp was ~30 and ~1 mg/g fresh weight, respectively. α-Mangostin was most abundant in the pericarp and fruit pulp with the molar ratio of α-mangostin to γ-mangostin in these tissues being approximately 6:1 and 9:1, respectively (Fig. 2).

3.2 Digestive stability, and bioaccessibility of xanthones

Recovery of α- and γ-mangostin after simulated gastric and small intestinal digestion of pericarp or fruit pulp exceeded 90 ± 2%. Approximately 70% of these xanthones partitioned into the filtered aqueous fraction during digestion of pericarp and fruit pulp (Fig. 3). Deletion of bile extract during small intestinal phase of digestion significantly decreased the concentrations of α- and γ-mangostin in the aqueous fraction to <10% of total in digesta (Fig. 3), suggesting that the majority of mangostin partitioned in micelles during small intestinal digestion.

3.3 Uptake, metabolism, and transport of xanthones by Caco-2 cells

The micelle fraction generated during simulated digestion was diluted with basal DMEM and added to monolayers of Caco-2 cells adhered to plastic to examine cellular accumulation of xanthones. The concentration of micellarized α- and γ-mangostin in test medium was 83.8 ± 5.9 and 17.3 ± 1.0 μmol/L for samples generated during digestion of pericarp and 7.7 ± 0.03 and 1.6 ± 0.2 μmol/L for samples from fruit pulp, respectively. Recovery of these compounds from medium added to wells without Caco-2 cells was 95.1 ± 2.6% after 6 h demonstrating the stability of the mangostin compounds in medium. Cellular content of α-mangostin after incubation for 4 h in medium containing micelles generated during small intestinal digestion of pericarp and fruit pulp was 17.2 ± 0.3 nmol/mg protein (20.5 ± 0.6% of total) and 3.3 ± 0.1 nmol/mg protein (19.0 ± 1.1% of total) ($p > 0.05$), respectively (Fig. 4). Similarly, the concentration of γ-mangostin in cells incubated with the same medium with micelle fraction from digested pericarp and pulp for 4 h was 2.2 ± 0.2 nmol/mg protein (29.0 ± 0.8% of total) and 0.2 ± 0.04 nmol/mg protein (15.1 ± 2.2% of total) ($p < 0.05$), respectively. Cells only retained 50–66% of α- and γ-mangostin after overnight incubation in medium without xanthones suggesting metabolism, efflux and/or degradation (Fig. 4). Analysis of medium added to cultures pretreated with α-mangostin contained both free and conjugated α-mangostin after 1, 2, and 16 h (see below).

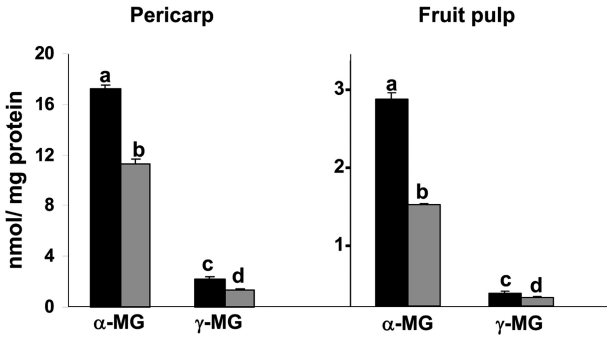

Figure 4. Uptake (black bar) and retention (gray bar) of xanthones from digested pericarp and fruit pulp of mangosteen by Caco-2 human intestinal cells. Cultures of Caco-2 cells were incubated with test media containing micelle fraction generated during simulated digestion of the pericarp and fruit pulp of mangosteen for 4 h before incubating cells in fresh medium without xanthones for 16 h. Data are means ± SD; $n = 6$. Means without a common letter above error bar differ significantly ($p < 0.05$).

Cellular accumulation of α-mangostin from digested pericarp and fruit pulp was proportional to the concentration in medium within the range of 2.0 – 84 nmol/mL ($r = 0.971$ and 0.999, respectively; $p < 0.05$) (Fig. 5). Similarly, Caco-2 cells accumulated γ-mangostin from digested pericarp and pulp in a dose dependent manner when medium concentrations ranged from 0.25 to 17.6 nmol/mL ($r = 0.925$ and 0.944, respectively; $p < 0.05$) (Fig. 5). However, maximum accumulation of α- or γ-mangostin was observed by 1 h and only 70% of the initial quantities of these xanthones added to medium was detected in cultures after 4 h. These results further suggested efficient cellular metabolism, efflux, or degradation.

Caco-2 cells were next grown on permeable membrane inserts to examine metabolism and transport of α-mangostin. The concentration of α-mangostin in the apical compartment decreased continuously in cultures incubated in medium containing oleate: taurocholate micelles to simulate prandial-like conditions (Fig. 6). This change was associated with a linear increase in the concentration of free α-mangostin in the basolateral compartment from 0.5 to 4 h. The intracellular concentration of α-mangostin in cells reached a maximum by 1 h and remained significantly ($p < 0.05$) greater than that in the basolateral compartment throughout the 6 h period of exposure. Treatment of medium with glucuronidase from *H. pomatia* revealed that phase II conjugates of α-mangostin accumulated in both the apical and basolateral compartments in a time-dependent manner. Such metabolites were not detected in cells. The distribution of free plus conjugated α-mangostin in the apical, cellular, and basolateral compartments after 6 h was 79.7 ± 2.5, 11.8 ± 2.2, and 8.5 ± 1.7%, respectively. Total recovery of α-mangostin in wells ranged from 98 to 101%. These data indicate that approximately one-third of α-mangostin initially added to the apical compartment was conjugated by 4 – 6 h and that the compound and its phase II metabolites were stable. Deletion of oleate/taurocholate micelles from mangostin-containing medium added to the apical compartment decreased free α-mangostin transported to the basolateral compartment by 50% ($p < 0.05$). In contrast, conjugated α-mangostin was not significantly different ($p > 0.05$) from that in the basolateral compartment in cultures receiving medium with the oleate/taurocholate micelles.

To examine the basolateral to apical flux of α-mangostin, medium containing 60 nmol α-mangostin and no mangostin was added to the basolateral and apical chambers, respectively. Transport of α-mangostin from basolateral chamber to cells and into the apical chamber was limited as compared to its transepithelial transport when α-mangostin was added to the apical chamber. After 3 h, cells contained 0.91 ± 0.04% of α-mangostin (55% free and 45% conjugated) in wells and only 1 nmol was transferred to the apical chamber (75% free and 25% conjugated).

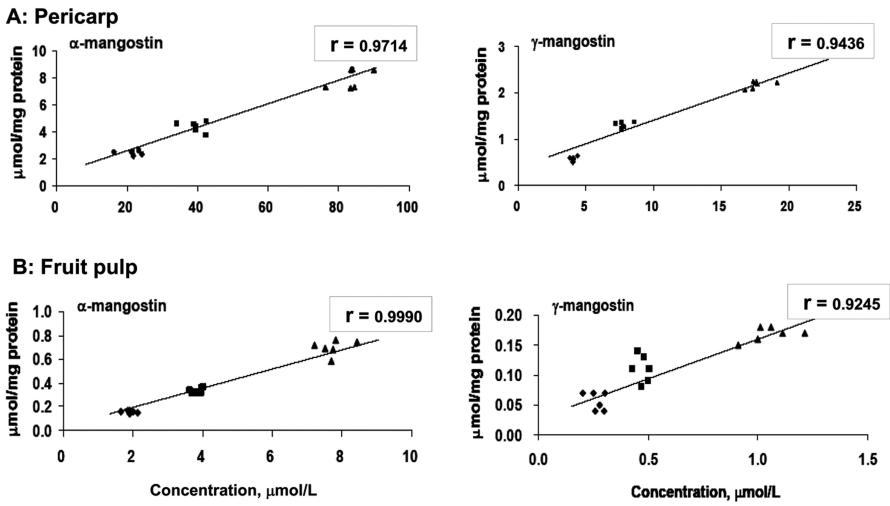

Figure 5. Cellular accumulation of α- and γ-mangostin from micellar fraction generated during simulated digestion of (A) pericarp and (B) fruit pulp of mangosteen is proportional to extracellular concentration. Data are mean ± SD, $n = 6$.

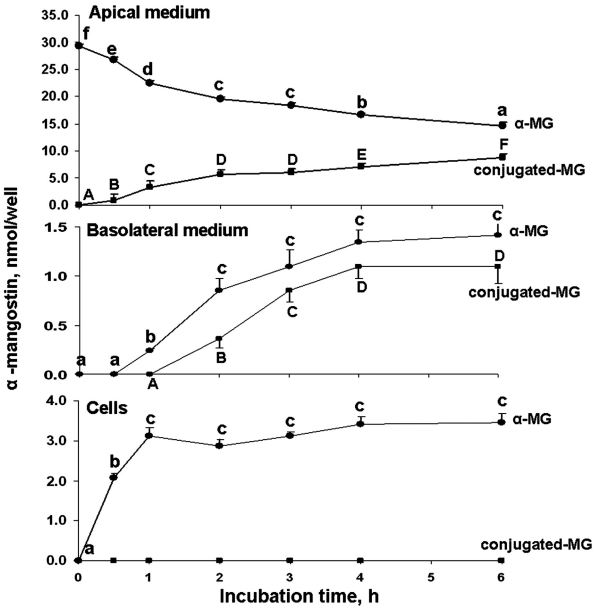

Figure 6. Transport and metabolism of α-mangostin by Caco-2 cells. Medium containing 28.6 nmol α-mangostin was added to apical compartment. Apical and basolateral media and cells were collected at indicated times to determine amounts of free (α-mangostin) and conjugated-mangostin as described in Section 2. Data are mean ± SD; $n = 5$. Means without a common letter above error bar differ significantly ($p < 0.05$).

4 Discussion

The absorption of bioactive food components generally is affected by stability of the ingested compound during digestion, delivery of the compound, or its active metabolite(s) to absorptive epithelial cells lining the gastrointestinal tract, uptake across the apical surface of intestinal epithelial cells, possible metabolism within epithelial cells, and transport of the ingested compound and its active metabolites across the basolateral membrane for distribution to target tissues. To our knowledge, this is the first study to assess the bioavailability of α- and γ-mangostin, the most abundant xanthones in the pericarp and fruit pulp of mangosteen. We used the coupled *in vitro* digestion and Caco-2 human intestinal cell model to examine various processes associated with the bioavailability of ingested compounds. The Caco-2 cell line has proved to be an excellent model for studies of intestinal uptake and absorption of nutrients, drugs, and other bioactive compounds [26, 27]. Differentiated Caco-2 cells express various cytochrome P450 isoforms, phase II enzymes including UDP-glucuronosyltransferases, sulfotransferases and glutathione-*S*-transferases, and effluxers on both the apical and basolateral membranes, thereby facilitating the investigation of presystemic metabolism [28, 29].

The qualitative and quantitative profiles of α- and γ-mangostin in digested pericarp and fruit pulp were quite similar to those in mangostin tissues and transfer of the xanthones to the aqueous fraction during digestion was relatively efficient (>50%). Omission of bile extract during the small intestinal phase of digestion significantly decreased the concentrations of α- and γ-mangostin in the aqueous fraction to <10%. This suggests that the majority of mangostin partitions in micelles as do most other fat soluble compounds during the small intestinal phase of digestion.

Differentiated cultures of Caco-2 cells grown on a plastic substratum accumulated 15–30% of α- and γ-mangostin from medium containing filtered aqueous fraction generated during simulated digestion during exposure period of 4 h. Uptake was directly proportional to concentration in medium. However, maximum cellular concentration peaked by 1 h and only 50–66% of intracellular α- and γ-mangostin was retained after overnight incubation in fresh medium without xanthones. Identification of free and conjugated α-mangostin in medium of washed cells preexposed to the xanthone supported the conclusion that some α-mangostin was metabolized by one or more phase II enzymes and these metabolites and free xanthones were effluxed across the apical membrane. Transport and metabolism were directly assessed using cells cultured on membrane inserts. Results showed that following apical uptake, some α-mangostin was transported to the basolateral compartment and another portion was conjugated to glucuronide or sulfate derivatives and effluxed into both the apical and basolateral compartments in a time dependent manner. Efflux of the conjugates across the apical membrane was more efficient than across the basolateral membrane as the amount of conjugated α-mangostin in the apical compartment was seven-fold greater quantity than that present in the basolateral compartment. After 6 h, approximately 9% of total α-mangostin (free plus conjugated) was present in the basolateral compartment. The extent of phase II metabolism of ingested compounds is dependent on structure. For example, Caco-2 cells readily convert free flavonoids such as quercetin, apigenin, luteolin, and chrysin to phase II conjugates [30, 31], whereas metabolism of the isoflavonoids genistein and daizein is quite limited [32]. As the snail enzyme used to convert conjugates in medium to the free xanthone possesses both glucuronidase and sulfatase activity (β-glucuronidase type HP-2 from *Helix pomatia*, product number G 7017, lot number 087K3806, Sigma–Aldrich, Missouri), information about the relative amounts of these conjugates and the locations of derivatized hydroxyl groups will require further investigation. Recovery of α-mangostin equivalents exceeded 95%, suggesting minimal, if any, methylated and glutathionylated derivatives [33, 34]. Because the Caco-2 cell system is closed, molecules transported into the apical and basolateral compartment may be retro-transported back into the cell. With the gastrointestinal lumen, the microflora can deconjugate effluxed phase II metabolites regenerating the dietary compound for transport into the intestinal cell [35]. We are not

aware of any reports that Caco-2 cells either express or secrete such catalytic activity on or across the basolateral membrane. Also, uptake of free α-mangostin from the basolateral compartment into the cell was only 1% that for apical uptake. Thus, both free and conjugated forms of α-mangostin accumulated in the basolateral compartment following efflux from the cell suggesting their absorption for delivery to peripheral tissues in humans. Nanomolar levels of free α-mangostin were recently reported in plasma of subjects after ingesting a commerical juice containing mangosteen and vitamins [36].

Efficient transfer of α- and γ-mangostin from the fruit matrix to the aqueous fraction required the presence of bile salts. Likewise, transepithelial transport of free, but not conjugated, α-mangostin was enhanced by adding oleate–taurocholate micelles to medium to simulate prandial-like conditions. Oleate is known to induce synthesis and secretion of chylomicrons by Caco-2 cells and *in vivo* [25]. Our data show that α-mangostin and likely other prenylated xanthones are processed in the intestine in a manner similar to that described for vitamin E [37] and retinol [38] as some free α-mangostin was transferred across the basolateral membrane in the absence of exogenous fatty acid. Prandial-like conditions result in transfer of α-tocopherol by chylomicron-dependent as well as HDL-dependent pathways, whereas dietary fat promotes absorption of retinyl esters in chylomicrons in addition to free retinol by a chylomicron-independent process. In contrast, absorption of more hydrophobic compounds such as β-carotene and lutein require incorporation into chylomicrons for basolateral efflux [21, 39]. These initial observations in the model system support the likelihood that the bioavailability of xanthones is increased when magosteen fruit and its products are ingested with a meal containing fat.

The absorption of methoxylated dietary flavonoids has been shown to exceed that of lesser or unmethoxlyated compounds with similar structures [40]. The difference has been associated with the increased metabolic stability that promotes bioavailability rather than conjugation and rapid efflux across the apical membrane. Mangosteen contains several xanthones with multiple methoxyl groups in addition to the mono-methoxylated α-mangostin [2]. Comparison of the relative bioavailability of methoxylated mangostins and nonmethoxylated xanthones in mangosteen merits investigation to further evaluate the impact of structure on biotransformation and relative bioavailability.

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The authors have declared no conflict of interest.

5 References

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