RESEARCH ARTICLE

Pharmacokinetics of α-mangostin in rats after intravenous and oral application

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Scope: The xanthone α-mangostin is one of the major bioactive secondary metabolites in *Garcinia mangostana*. Until now, *in vivo* studies on the absorption, bioavailability, disposition, and metabolism of α-mangostin are limited.

Methods and results: In the present study, an LC-MS/MS assay has been established for the determination of α-mangostin in rat plasma. The validated method was used successfully to support pharmacokinetic studies in rats after intravenous (i.v.) and oral administration. Both non-compartmental and compartmental analyses were performed, where the two-compartment body model had a good fit with the i.v. data. Following i.v. administration, the disposition of α-mangostin in rat plasma was biphasic, subdivided into a fast distribution and a slow elimination phase. The half-life of the distribution phase was 3 min, and that of the terminal elimination phase 3.5 h, indicating a high tissue binding. However, for oral administration, the bioavailability was so low that it was not possible to obtain a full concentration–time profile.

Conclusion: Although pure α-mangostin has shown a variety of pharmacological activities in *in vitro* assays at present it is uncertain if the same magnitude of effects will be achieved *in vivo* when its low bioavailability is considered.

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1 Introduction

Garcinia mangostana L. (Clusiaceae) is a tropical evergreen fruit tree also known as mangosteen. It is believed to originate from Southeast Asia and is mainly found in Thailand, Myanmar, Malaysia, Indonesia, and Singapore [1]. Different parts of mangosteen, mostly the pericarp, the leaves, and the bark have been used traditionally for a variety of medical conditions, such as arthritis, diarrhea, dysentery, inflammation, and skin disorders, and have also been utilized for their wound-healing properties [2, 3]. Recently, extracts obtained from the pericarp of mangosteen exhibited a variety of biological properties *in vitro*, such as antioxidant [4–6], cytotoxic [7], anti-inflammatory [8], antibacterial [9], antifungal [10], antiviral [11, 12], and cancer chemoprevention-related effects [13, 14]. The major bioactive compounds in mangosteen are xanthone derivatives, and α-mangostin is the first such substance to be isolated [2, 3, 15, 16]. Like other xanthone derivatives, α-mangostin has a tricyclic aromatic ring system [17], and is present in the

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Abbreviations: AIC, Akaike criteria; **AUC,** area under the curve; **AUMC,** area under the first moment curve; **CL,** clearance; **HC,** high concentration; **IS,** internal standard; **LC,** low concentration; **MC,** medium concentration; **PK,** pharmacokinetic; **%RE,** relative error; **QC,** quality control; **SC,** Schwartz criteria; **TSQ,** Triple Stage Quadrupol; **WSSR,** weighted sum of square of residuals

dried mangosteen pericarp at concentrations up to 5.5 mg/g [18]. α-Mangostin has been reported to have all the pharmacological activities of mangosteen extracts [12, 19–22]. However, most of the data have been generated using *in vitro* assays. Only very few of the mentioned effects have been confirmed in animal studies [23–25]. In that context, the lack of clinical data is a serious deficit. It remains to be clarified to what extent the findings about pharmacological activities are of potential clinical relevance.

Because of the promising *in vitro* data from α-mangostin and other xanthone derivatives, extracts and pure compounds derived from mangosteen have been commercially used as a botanical supplement. The consumption of those supplements has been increased dramatically in the United States and mangosteen fruit juice was ranked as one of the top five-selling ''single botanicals'' on the U.S. market in 2008 (http://nutritionbusinessjournal.com). Not only the juice but also tablets made from extracts or pure compounds can be purchased online and in herbal shops. For assessment of quality, safety, and efficacy of mangosteen products, there is a need for quantitative data regarding absorption, metabolism, and other pharmacokinetic (PK) properties of α-mangostin. Up to now, a single report on bioavailability of α-mangostin in humans after ingestion of a xanthone-rich liquid preparation has been published [26]. However, no data exist about the absolute bioavailability of α-mangostin. Therefore, the objective of our study was to evaluate the PKs of α-mangostin after oral and i.v. administration in rats. Since the concentration of metabolites in biological samples is very low, a sensitive and specific assay method was crucial for their identification. In the present study, a simple and rapid reversed-phase high-performance liquid chromatographic method with triple quadrupole mass spectrometer (LC-MS/MS) detection has been proven to be a useful tool to determine concentrations of α-mangostin in rat plasma samples.

2 Materials and methods

2.1 Chemicals and reagents

α-Mangostin used for this study was extracted and purified from the fruits of *G. mangostana*, as described previously [5]. A reference standard of α-mangostin (purity 96.5%) was purchased from ChromaDex (Irvine, CA, USA). Bergamottin (purity 98%), which was used as internal standard (IS), was purchased from Indofine Chemical Company (Hillsborough, NJ, USA). Figure 1 shows the structure of both compounds. ACN (HPLC grade), formic acid, and sodium chloride were purchased from Fisher Scientific (Pittsburgh, PA, USA). Ethanol (HPLC grade), Tween 80, glucose, and heparin sodium salt (202 unit/mg) were obtained from Sigma (St. Louis, MO, USA). Distilled water was purified before use with a Barnstead Nanopure Diamond UV ultra-pure water system (Dubuque, IA, USA).

2.2 Instrumentation and LC-MS/MS conditions

The LC-MS/MS system consisted of a Surveyor HPLC autosampler, Surveyor MS quaternary pump, and a Triple Stage Quadrupol (TSQ) Quantum Discovery triple quadrupole mass spectrometer (ThermoFisher Scientific, San Jose, CA, USA). The instrument was controlled by Xcalibur software (Version 1.4). The samples were analyzed at room temperature. The TSQ Quantum was equipped with an electrospray ionization (ESI) source and operated in the positive-ion mode. The instrument parameters were as follows: spray voltage set to 4.0 kV and source CID 12 V. The instrument parameters included an ion transfer tube temperature of 325°C, spray voltage of 5.0 kV, and source CID set to 5 V. Nitrogen was used as the sheath and auxiliary gas and set to 35 and 10 (arbitrary units), respectively. The collision energy was 27 eV for α-mangostin and 22 eV for bergamottin. The instrument was operated in resolution mode with the peak width (full width at half-maximum, FWHM) set to 0.7 *m/z* both at Q1 and Q3. The selected reaction monitoring scheme followed transitions of the precursor to selected product ions with the following values: *m/z* 411 → 355 for α-mangostin and *m/z* 339 → 202 for bergamottin. Chromatography was performed on a Symmetry C18, 4.6 mm × 2.0 mm, 3.5 um analytical column (Waters, Milford, MA, USA). The mobile phase consisted of 0.05% formic acid in ACN:water (80:20, v/v) delivered at a flow rate of 0.5 mL/min (injection volume 50 μL).

2.3 Sample preparation

The stock solutions of α-mangostin and bergamottin were prepared in ACN at a concentration of 4 mg/mL. The IS

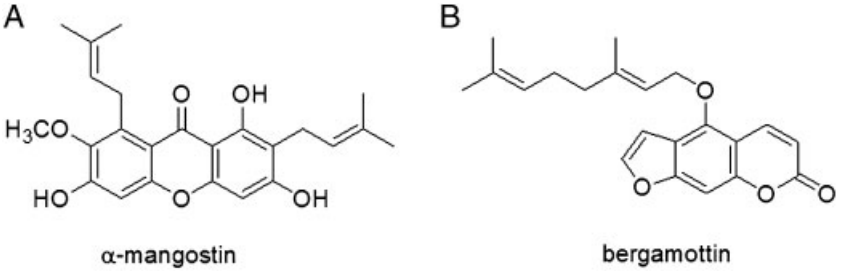

Figure 1. Structures of α-mangostin (A) and the IS bergamottin (B).

solution was prepared by diluting the bergamottin stock solution in methanol:ACN (25:75, v/v) to produce the final concentration of 200 ng/mL. Bergamottin was chosen as an IS since it is not present in *G. mangostana* plant material; it is commercially available and has a similar molecular weight as α-mangostin. From the 20 tested IS candidates, best results were obtained with bergamottin. Working solutions of α-mangostin with concentrations in the range of 4–1000 μg/mL were obtained by diluting the stock solution with ACN:water (50:50, v/v). The calibration standards were prepared by spiking blank rat plasma samples (1 mL) with the corresponding working solution (5–10 μL) to yield seven concentrations ranging from 20 to 2000 ng/mL. For validation, quality control (QC) samples were prepared in the same way as the calibration standards at three concentrations (low concentration (LC) = 70, medium concentration (MC) = 850, and high concentration (HC) = 1800 ng/mL). Also, dilution QC samples at 10000 ng/mL were prepared and then diluted with blank plasma at 1:10 ratio (called Dil-QC samples). Plasma samples (50 μL) were mixed with 200 μL IS solution, and centrifuged at 13.2×1000 rpm for 15 min at room temperature. The supernatant was then transferred to autosampler vials and 50 μL of sample were injected into the LC-MS/MS system for analysis.

2.4 Method validation

The method was fully validated for recovery, matrix effect, linearity, selectivity precision, and accuracy according to the United States Food and Drug Administration (FDA) Bioanalytical Method Validation Guidance [1]. Extraction efficiencies were determined by comparing the peak areas of QC samples with those of the blank rat plasma samples spiked with compound after extraction. Matrix effects were determined by comparing the peak areas of blank rat plasma samples spiked with compound after extraction with those of the inject solution spiked with compound. The freeze–thaw stability was determined by thawing at room temperature and refreezing at −20°C QC (LC, MC, and HC) samples for three cycles, and expressed as accuracy in relation to the nominal concentration. Post-preparative stability and plasma stability was assessed with five groups (control, room temperature for 6 h, 24 h plasma stability, 24 h autosampler stability, 24 h stability in refrigerator). The stability was assessed by comparing the mean and SD of peak area ratio of α-mangostin to bergamottin within groups.

2.5 PK study

Male Sprague Dawley rats with jugular vein catheters (weighing between 320 and 350 g) were purchased from Charles River (Wilmington, MA, USA). The animals were single-housed in plastic cages and received a standard chow and water ad libitum during the experiments. All the animals were maintained on a 12 h/12 h light/dark cycle. Non-fasted animals were used for the study. All animal experiments were performed according to the policies and guidelines of the Institutional Animal Care and Use Committee (IACUC) of the University of Florida, Gainesville, USA (NIH publication # 85–23), study protocol # 200802291.

The same rats were used for the intravenous (i.v.) and oral study; they first received α-mangostin at 2 mg/kg i.v. and after a washout period of 1 wk, 20 mg/kg orally. α-Mangostin was dissolved in an aqueous solution containing 2% ethanol and 2% Tween 80. Blood samples (500 μL) were collected from the sublingual vein into Vaccuette® heparinized tubes 0 (prior to dosing), 2, 5, 10, 20, 30 min, 1, 2, 4, and 6 h. The loss of blood volume was replaced with 1 mL normal saline. Blood samples were centrifuged at 4000 rpm for 15 min at 4°C. Plasma samples were then transferred into 1.5 mL tubes and stored at −20°C until analysis. For analysis, 50 μL plasma samples were mixed with 200 μL IS solution, and centrifuged as described before. The supernatant was then transferred to autosampler vials and 50 μL of sample was injected into the LC-MS/MS system for analysis.

2.6 Data analysis

Mean plasma concentrations of α-mangostin after i.v. administration *versus* time curve were generated in Graphpad Prim (version 5.01, San Diego, CA, USA). The PK parameters were determined by non-compartmental and compartmental analysis using WinNonlin software (version 5.2.1, Pharsight, St. Louis, MO, USA).

Non-compartmental PK: The PK parameters determined were the concentration at time 0 (C_0), the terminal elimination rate constant (K_e), the terminal elimination half-life ($t_{1/2}$), the area under the curve (AUC), the area under the first moment curve (AUMC), the mean residence time (MRT), the volume of distribution at terminal phase (V_z), and the clearance (CL). $AUC_{0\rightarrow last}$ was calculated using a linear/log trapezoidal method from time 0 to the last sampling point 6 h after administration. The terminal phase to calculate K_e was specified to the range from 0.5 to 6 h after administration, and K_e was calculated by linear regression of the terminal log linear phase.

Compartmental PK: The α-mangostin concentration–time profile was tested in two-compartment body models and three-compartment models with different weighting factor, and the goodness of fit was determined by the AIC (Akaike criteria), SC (Schwartz criteria), and WSSR (weighted sum of square of residuals). The lower the AIC, SC, and WSSR the more appropriate is the selected model. PK parameters were calculated using the selected two-compartment body model with the Gauss–Newton minimization method [27]

and weighting factor as $1/\hat{Y}^2$. The equation for a two-compartment model is as follows: $C = A^*e^{-\alpha t} + B^*e^{-\beta t}$ where C is the concentration of drug in plasma at time t; A and B are mathematical coefficients; α is the distribution rate constant; β is the terminal phase rate constant; and t is the time. Parameters both from non-compartmental and compartmental evaluation were under descriptive statistical analysis using WinNonlin software to calculate the mean and standard error (SE).

3 Results

3.1 Method development and validation

The LC-MS/MS method was developed to analyze α-mangostin in rat plasma samples. Blank rat plasma was used for the validation and the corresponding chromatogram is shown in Fig. 2A. In Fig. 2B plasma samples spiked with bergamottin as IS are displayed. The retention times were approximately 4.72 and 5.07 min for α-mangostin and bergamottin, respectively.

The method was validated by evaluating recovery, matrix effect, linearity, precision, accuracy, and stability [1]. The extraction recovery of α-mangostin using protein precipitation was expressed as the ratio of the mean peak area of extracted plasma QC samples (LC, MC, and HC) to the mean peak area of the blank plasma samples spiked with compound after extraction. The recovery percentages were 90.8, 92.1, and 96.6% at concentrations of 70, 850, and 1800 ng/mL, respectively (Table 1). The matrix effect of

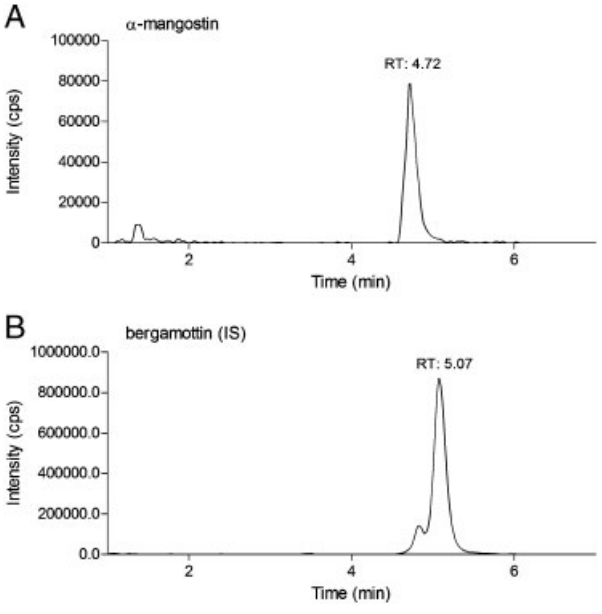

Figure 2. The extracted LC-MS/MS chromatograms of (A) plasma sample from a rat obtained 10 min after i.v. administration of α-mangostin (concentration = 695.1 ng/mL) and (B) bergamottin (200 ng/mL) as the IS.

Table 1. Extraction efficiency and matrix effect of α-mangostin and bergamottin

Nominal concentration (ng/mL)	Mean extraction recovery ($n = 6$) (%)	Mean matrix effect ($n = 6$) (%)
α-Mangostin		
70	90.8	123.1
850	92.1	118.6
1800	96.6	112.3
Bergamottin		
200	99.6	171.3

Table 2. Intra-assay ($n = 8$) and inter-assay ($n = 24$) precision and accuracy for analysis of α-mangostin in rat plasma

		QC samples (ng/mL)			
		70 (%)	850 (%)	1800 (%)	10 000 (%)
Accuracy	(%RE)	10.2	7.3	7.9	7.1
Precision	Intra-run (%RSD)	12.8	8.9	7.9	7.6
	Inter-run (%RSD)	13.2	9.1	8.6	8.6

α-mangostin in plasma was expressed as the ratio of the mean peak area of blank plasma samples spiked with compound at three-level QC concentrations after extraction with the mean peak area of the injected solution spiked with compound at the same concentration. No significant matrix effects were observed for α-mangostin, but these were evident for bergamottin in rat plasma (Table 1). The calibration curves of α-mangostin were constructed by plotting peak area ratio of α-mangostin/bergamottin to the concentration of α-mangostin. Calibration curves were linear within the concentration range of 20–2000 ng/mL with a mean ± SD correlation coefficient (R^2) of 0.9892 ± 0.0034. The LLOQ for α-mangostin in plasma was defined as 20 ng/mL, as it was the lowest concentration on the calibration curve. To extend the highest limit of the calibration curve, Dil-QC samples were prepared by spiking blank plasma with α-mangostin at 10 000 ng/mL and then diluted with blank plasma at 1:10 ratio. Intra-run precision and accuracy were determined by performing an eight-replicate analysis of QC (LC, MC, HC, and Dil-QC) samples on the same day, and expressed as relative standard deviation (%RSD) and relative error (%RE). The same procedure was performed for 3 days to determine the inter-run precision. At the LLOQ, the accuracy (%RE), intra- and inter-run precision (%RSD) were 12.7, 16.3, and 15.6%, respectively. The inter- and intra-run precision and accuracy for α-mangostin at LC, MC, HC, and Dil-QC concentrations are summarized in Table 2. The freeze–thaw stabilities of α-mangostin were assessed by performing a

four-replicate-analysis of LC, MC, and HC samples. α-Mangostin was stable after three freeze–thaw cycles as the %RE with respect to nominal concentration was 13.8, 6.4, and 6.9% for LC, MC, and HC, respectively. The post-preparative stability and plasma stability were assessed by performing eight replicate analyses of LC and HC samples. The peak area ratio of α-mangostin to bergamottin showed no significant changes when the plasma samples had been stored at room temperature for 24 h before or after extraction, on comparing to the plasma samples stored in the freezer and extracted prior to analysis (data not shown). Overall, the stability of α-mangostin was found to be reasonable.

3.2 PK study of α-mangostin in rats

A validated method was used successfully to support the PK study of α-mangostin in rats after a single i.v. dose of 2 mg/kg. Table 3 summarizes the main PK parameters of α-mangostin calculated by non-compartmental analysis using WinNonlin software. Following i.v. administration, the maximum concentration of α-mangostin was 17.88 μg/mL at time 0 calculated from non-compartmental analysis. K_e was 0.26 l/h, and the $t_{1/2}$ was 2.97 h calculated by $0.693/K_e$. The mean plasma concentration *versus* time profile after i.v. administration was biphasic, subdivided into a distribution phase and a slow elimination phase, as shown in Fig. 3A. The two-compartment body model with the weighting factor $1/Y^2$ described the data well, as the AIC, SC, and WSSR were 1.24, 2.02 and 0.51, respectively. Also, the goodness of fit can be seen in Fig. 3B, which shows the simulated concentration *versus* time profile with the two-compartment body model in each subject. PK parameters of a two-compartment body model are summarized in Table 4. As expected, the rate constant in the slow elimination phase (β) was 0.26 l/h, equal to the K_e calculated from non-compartmental analysis, and the same as the $t_{1/2}$. The half-life of the distribution phase was 0.05 h, suggesting that after 3 min, half of the compound had been cleared already from the plasma. The values of AUC, AUMC, MRT, and CL of the compartmental analysis were close to the ones obtained with the non-compartmental analysis. The C_0 of the compartmental analysis was 10.22 μg/mL, which is lower than the C_0 of the non-compartmental analysis. This is most likely caused by the weighting factor $1/Y^2$ used in the compartmental analysis, as it emphasized the factor of the low concentration in the calculation.

Table 3. PK parameters after a single intravenous dose of 2 mg/kg α-mangostin in rats ($n = 8$)[a)]

Parameters[b)]	Mean	SE
C_0 (ng/mL)	17880	4432
K_e (1/h)	0.26	0.03
$t_{1/2}$ (h)	2.97	0.38
AUC_{0-6} (ng*h/mL)	1233	157.1
$AUC_{0-\infty}$ (ng*h/mL)	1372	140.4
$AUMC_{0-6}$ (ng*h*h/mL)	791.3	63.84
$AUMC_{0-\infty}$ (ng*h*h/mL)	2335	434.2
MRT (h)	1.85	0.39
V_z (L/kg)	6.82	1.10
CL (L/h/kg)	1.54	0.12

a) Data were calculated using non-compartmental analysis.
b) AUC_{0-6} = AUC from time 0 to 6 h; $AUC_{0-\infty}$ = AUC with extrapolation; $AUMC_{0-6}$ = AUMC from time 0 to 6 h; $AUMC_{0-\infty}$ = AUMC with extrapolation.

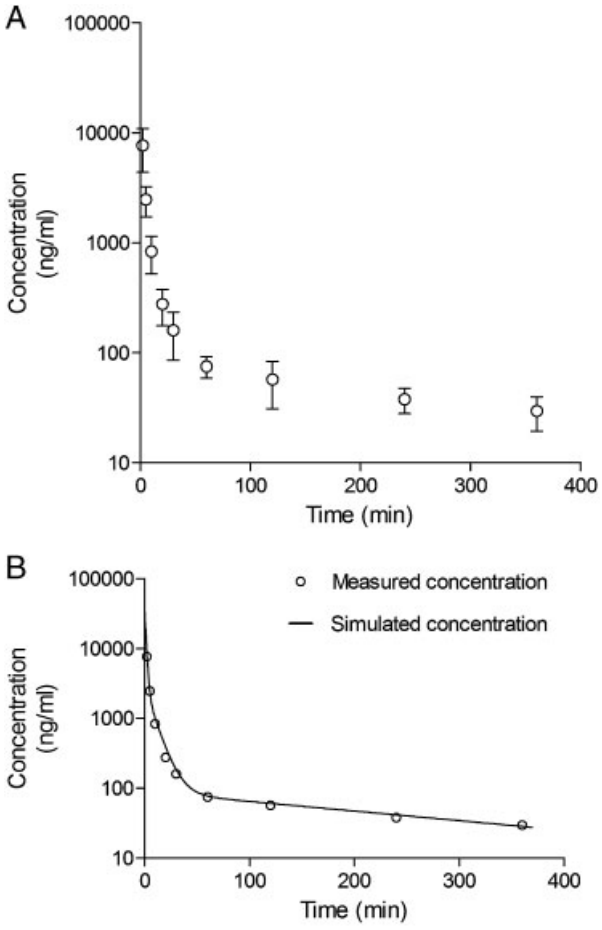

Figure 3. (A) Mean concentration–time profile for α-mangostin in rat plasma after a single i.v. dose of 2 mg/kg ($n = 8$). (B) Simulated concentration–time profile after i.v. administration of 2 mg/kg α-mangostin using a two-compartmental body model.

A single oral dose of 20 mg/kg was also given to the same rats after a washout period of 1 wk. However, 10 min after administration, the concentration of α-mangostin in rat plasma was already lower than the LLOQ, and remained at this low level at least until 12 h after administration (Fig. 4). Thus, it was not possible to obtain a full concentration–time profile of α-mangostin after oral administration to calculate the value of absolute bioavailability.

Table 4. PK parameters after a single intravenous dose of 2 mg/kg α-mangostin in rats ($n = 8$)[a)]

Parameters[b)]	Mean	SE
A (ng/mL)	10 216	1849
B (ng/mL)	136.5	34.1
α (1/h)	14.2	1.39
β (1/h)	0.26	0.05
K_{10} (1/h)	8.24	0.97
K_{12} (1/h)	5.81	0.66
K_{21} (1/h)	0.45	0.07
C_0 (ng/mL)	10 353	1879
$AUC_{0-\infty}$ (ng*h/mL)	1237	111.2
$AUMC_{0-\infty}$ (ng*h*h/mL)	2874	852.0
MRT (h)	2.36	0.62
V_c (L/kg)	0.23	0.03
V_p (L/kg)	3.76	0.91
CL (L/h/kg)	1.70	0.13
$t_{1/2\alpha}$ (h)	0.05	0.01
$t_{1/2\beta}$ (h)	3.46	0.74

a) Data were fitted into a two-compartment model.

b) K_{10} = elimination rate constant of central compartment; K_{12} = transfer rate constant from central compartment to peripheral compartment; K_{21} = transfer rate constant from peripheral compartment to central compartment; $AUC_{0-\infty}$ = AUC with extrapolation; $AUMC_{0-\infty}$ = AUMC with extrapolation; V_c = volume of distribution of central compartment; V_p = volume of distribution of peripheral compartment; $t_{1/2\alpha}$ = half-life of distribution phase; $t_{1/2\beta}$ = half-life of elimination phase.

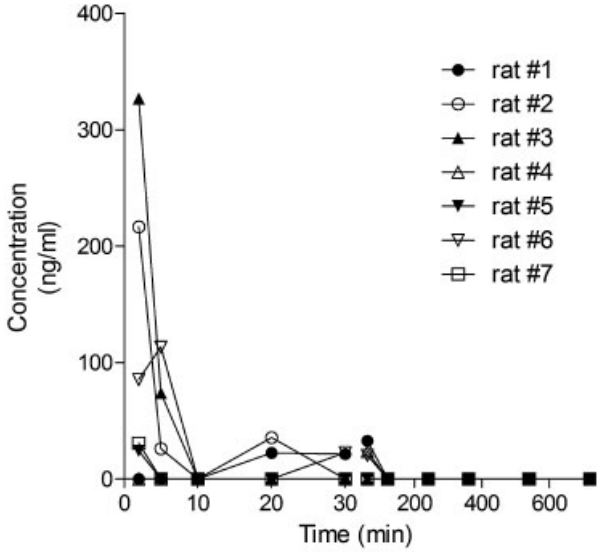

Figure 4. Plasma concentration–time profile for α-mangostin in rat plasma after a single oral dose of 20 mg/kg.

4 Discussion

Although in recent years the number of *in vitro* studies investigating the pharmacodynamic effects of preparations obtained from *G. mangostana* as well as selected xanthones such as α- and γ-mangostin has increased rapidly, there is still limited information available regarding their PKs. Thus, the relevance of the *in vitro* activity to the therapeutic effects found in individual studies is still not established. The absorption, metabolism, and disposition of α-mangostin must be determined before any conclusion on the potential benefits of dietary or commercially available mangosteen products can be drawn. The lack of PK data might be due to the following reasons: the study of herbal PKs in general is extraordinarily complex because herbal preparations are multicomponent mixtures that contain numerous phytochemicals. Therefore, concentrations of single compounds in the final product are in the lower mg range *per* dose. The resulting plasma concentrations are often in the μg to pg *per* liter range. As a consequence, analytical methods determining bioavailability and PKs of herbal preparations have to be sufficiently sensitive. In the present study, a simple, rapid, and fully validated LC-MS/MS method has been developed for the determination of α-mangostin in rat plasma. To our knowledge, this is the first time that a concentration–time profile of α-mangostin after i.v. administration has been obtained. Our data show that the PK profile of α-mangostin is biphasic, including a rapid distribution phase and a slow elimination phase. The half-life of 2.97 h can be associated to a large V_z (V_z = 6.82 L/kg) and attributable to a small plasma CL (CL = 1.54 L/h/kg). The high V_z of 6.82 L/kg suggests that the compound is taken up by body tissues rapidly. Compartmental analysis revealed that aparent volume of distribution in steady state (= V_c+V_p (V_c, volume of distribution of central compartment; V_p, volume of distribution of peripheral compartment)) is relatively high (3.99 L/kg), which suggests that possibly tissue-binding in the peripheral compartment causes the long half-life. This assumption is supported by the long $t_{1/2}$ of 3.46 h. This finding is potentially important since the purported health-promoting benefits of mangosteen compounds are dependent on delivery of these xanthones to target tissues. However, the present data show that the oral bioavailability of α-mangostin is extremely low in rats. The low plasma concentration achieved initially and the rapid drop indicate that α-mangostin undergoes an intensive first-pass metabolism.

In a recent study, Kondo *et al.* [26] investigated the bioavailability of a xanthone-rich mangosteen product in healthy volunteers after consumption of 59 mL of a supplement. The liquid administered contained mangosteen juice, aloe vera, green tea, compounds labeled as epigallocatechin-gallate (EGCG) and multivitamins. The total amount of xanthones in the product was 94.2 mg/dose (= 59 mL). However, the exact amounts of α- and γ-mangostin consumed were not reported. The maximum concentration of α-mangostin was 3.12 ng/mL with a t_{max} of 1 h after consumption of the supplement [26]. However, since the exact dose of α-mangostin before administration was not determined and only four time points were chosen for blood collection, the information that can be obtained on

the bioavailability of α-mangostin from this study is limited. In addition, it has to be considered that the supplement contained reasonable amounts of the polyphenol, epigallocatechin-gallate, as well as other vitamins. Thus, it can be rationalized that the bioavailability of α-mangostin might also be influenced by other components in the complex mixture that can act to improve the stability, solubility, or the half-life time of the active compounds. Examples in the literature have shown that such co-effectors improve not only the solubility but also the bioavailability of single compounds. For example, Butterweck *et al.* [28] demonstrated that polyphenols such as procyanidin B2 and hyperoside increased the oral bioavailability of the naphthodianthrone hypericin in rats by approximately 58% (B2) and 34% (hyperoside), respectively. Since in our present study the bioavailability of pure α-mangostin was too low to be determined but conversely the data of Kondo *et al.* [26] suggest that α-mangostin seems to be bioavailable when given in form of a supplement, it can be speculated that co-effectors may be necessary for the absorption of this compound. In this regard, Bumrungpert *et al.* [29] have come to a similar conclusion. The authors used Caco-2 cells to investigate the digestive stability, bioaccessibility, and intestinal cell transport of α- and γ-mangostin from digested pericarp and fruit pulp of mangosteen. 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 maximal by 1 h. These authors also demonstrated that in the absence of oleate/taurocholate micelles, the amount of free α-mangostin amount transported to the basolateral compartment decreased by 50%, suggesting that absorption is enhanced by dietary fat [29].

In conclusion, the present study represents the first evaluation of pure α-mangostin in rats after i.v. and oral administration. Our present data indicate that α-mangostin is rapidly eliminated from the blood and transferred to tissues after i.v. administration. A two-compartment model best describes the plasma profile of α-mangostin after i.v. administration.

It is suggested that the extremely low bioavailability of pure α-mangostin after oral administration in rats can be attributed to an intensive first pass metabolism. However, pure α-mangostin has shown several pharmacological activities in *in vitro* assays, but, based on our data revealing its low oral bioavailability, it is questionable if comparable activities will be realized in *in vivo* experiments. Since α-mangostin seems to be preferentially bioavailable from extract preparations or in the presence of dietary fat it will therefore be necessary to determine the oral bioavailability after administration of a clearly defined and quantified mangosteen extract. Further investigations in this direction including tissue distribution and elimination are currently in progress.

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