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RESEARCH ARTICLE

Biochemistry

Quantification of metabolite cinnamic acid of cinnamon (*Cinnamomum zeylanicum*) in human plasma

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Abstract: *Cinnamomum zeylanicum* (CZ) is known to have numerous beneficial medicinal effects. The mechanism of action and compounds which account for these effects are not yet clearly defined. The present study aims to develop and validate a method to quantify the metabolites of CZ in human plasma and study its pharmacokinetic profile. Cinnamic acid (CA) was identified as the main metabolites of CZ in human plasma and was used to develop and validate the method. HPLC with a UV-detector was used to identify and quantify CA. Linearity, precision, bias, repeatability, and lower limit of detection (LOD) were determined. CZ (5 g) was orally administered to 5 healthy volunteers and serial blood samples were taken, to determine maximal plasma concentration (C_{max}), time to reach maximal concentration (T_{max}) and elimination half-life ($T_{½}$) of CA. The precision, bias, and repeatability, of the method were 7.73%, 4.20%, and 5.63%, respectively. LOD was 1.11 µmol/L and samples were stable up to five days at 4 ºC. Recovery of the method was 95% -125%. The retention time of CA was 16 minutes at 254 nm. Concentrations of CA between 0.5 and 200.0 µmol/L in a plasma matrix showed a linear response. C_{max} was 1.9 ± 1.5 µmol/L, while T_{max} and $T_{½}$ were 15 and 36 minutes respectively. The study developed a sensitive and specific HPLC method to detect CA, a key metabolite of CZ in humans, which is suitable for human pharmacokinetic studies. These pharmacokinetic parameters (C_{max}, T_{max}, $T_{½}$) would help in further development of CZ as a pharmaceutical agent for use in humans.

Keywords: Ceylon cinnamon, *Cinnamomum zeylanicum,* HPLC, humans, pharmacokinetics.

INTRODUCTION

Cinnamon, a spice mainly used as a flavouring agent, belongs to the Lauracea family. It has been a constituent of our food since ancient times. Cinnamon is also used in the aroma and essence industries due to its fragrance. Many parts of the cinnamon tree such as the bark, leaves, flowers, fruits, and roots, have some medicinal or culinary use. At present, there are approximately 250 different species identified in the cinnamon genus (Sangal *et al*., 2011; Vangalapati & Prakash *et al.*, 2012) *Cinnamomum zeylanicum* (also known as *Cinnamomum verum*) and *Cinnamomum cassia* (*C. cassia* or *aromaticum*) are the two main species of cinnamon used all over the world (Ranasinghe *et al*., 2013). *Cinnamomum zeylanicum* (*C. zeylanicum*), well known as Ceylon cinnamon (derived from its Latin name, zeylanicum) or also referred to as 'true cinnamon' is indigenous to Sri Lanka and southern parts of India. Sri Lanka produces the largest quantity and best quality Ceylon/true cinnamon in the world (Ranasinghe *et al*., 2017).

In traditional Sri Lankan medicine, cinnamon is used as a remedy for respiratory, digestive, and gynaecological aliments (Ranasinghe *et al*., 2013). In recent times, *in vitro* and *in vivo* studies using both *C. zeylanicum* and *C. cassia* have demonstrated numerous beneficial medicinal effects. These include antimicrobial, anti-inflammatory, anti-parasitic, antioxidant, anti-diabetic, anti-cancer, cholesterol lowering and blood pressure lowering activities (Wondrak *et al*., 2010; Ranasinghe *et al*., 2013; Rao & Gan, 2014). However, it

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is important to note that most of the above effects were demonstrated *in vitro* and in animal studies, with few studies in humans (Khan *et al*., 2003; Bernardo *et al*., 2015). The mechanism of action and compounds which account for the medicinal effects are not yet clearly identified and require further study. Furthermore, since some of the demonstrated medicinal benefits include systemic effects, it is important to understand the pharmacokinetic profile of cinnamon in humans.

Cinnamon consists of a variety of resinous compounds, including cinnamaldehyde, cinnamate, cinnamic acid, and numerous essential oils (Senanayake *et al*., 2002). The amount of compounds present varies according to the part of the plant, with the bark having mainly cinnamaldehyde (65–80%) and eugenol (5–10%) (Rao & Gan, 2014). Each compound in cinnamon may or may not follow different pathways in the body after oral administration, forming different metabolites. Cinnamaldehyde, cinnamyl acetate, and cinnamyl alcohol are converted into cinnamic acid by oxidation and hydrolysis, and subsequently β-oxidized to benzoate in the liver (El-Mawla *et al.*, 2001; Brahmachari *et al*., 2009). Yuan *et al*. (1992) demonstrated that cinnamaldehyde follows first order kinetics with a half-life ($t_{1/2}$) of 9 min in rat blood and was almost completely metabolized into cinnamic acid before it was absorbed into blood. Several similar animal studies have been done to study the various pharmacokinetic parameters of cinnamon (Song *et al*., 2002; Chen *et al*., 2009). However, to date, there are no studies reporting the pharmacokinetic profile of *Cinnamomum zeylanicum* (CZ) in humans. Hence, the present study aims to develop and validate a method to quantify the metabolite of CZ in human plasma and study its pharmacokinetic profile after oral administration to healthy volunteers.

MATERIALS AND METHODS

Chemicals, reagents and instruments

Analytical grade cinnamic acid (purity ≥ 99%) (Sigma-Aldrich, St. Louis, MO, USA) was used for the study. In addition HPLC-grade acetonitrile (assay ≥ 99.8%) (Fisher Scientific, California, USA), methanol (assay ≥ 99.9%) (Sigma-Aldrich, St. Louis, MO, USA), ethyl acetate (assay ≥ 99.8%) (Sigma-Aldrich, St. Louis, MO, USA), and acetic acid (assay ≥ 99.8%) (Sigma-Aldrich, St. Louis, MO, USA) and hydrochloric acid (assay ≥ 37%) (Sigma-Aldrich, St. Louis, MO, USA) were used. The chromatographic system consisted of a PU-980 Jasco pump, a LC-800 series 802-SC system controller, LC-900 series CO-965 column, a UV-970 UV-vis detector set at 254 nm, a 20 µL injection loop, a workstation for data collection and a C18 HPLC column 250 mm × 4.6 mm × 5µm. The mobile phase was methanol : acetonitrile : 2% acetic acid (20:25:70 v/v) at a flow rate of 1 mL/min and it was operated at room temperature.

Development of HPLC analysis method

A stock solution of standard cinnamic acid (0.021 mol/L) was prepared using methanol and it was diluted with methanol to prepare working solutions of cinnamic acid (0.5–800 µmol/L). All prepared standard solutions were stored at 4 ^{o}C. Plasma samples were obtained from National Blood Transfusion Service at the National Hospital of Sri Lanka (Lot No: 15C008598). Aliquots of 25 mL from each one of the prepared serial dilutions of cinnamic acid (0.5–800 mmol/L) were added to each of the 250 mL samples of plasma to obtain the different concentrations of cinnamic acid in plasma. Plasma and cinnamic acid mixtures were vortexed for 2 min (Autovortex SA6 model, Stuart Scientific, UK).

Subsequently, for the purpose of extraction of cinnamic acid for HPLC analysis, each plasma sample with cinnamic acid was acidified with 75.0 µL of 0.1 mol/L HCl and then vortexed for 1 min; subsequently, 1.5 mL of ethyl acetate was added and it was vortexed for another 2 min. Then it was centrifuged at 2500 rpm for 10 min (Kubota Laboratory Centrifuge 5100 model, Japan) at room temperature and the supernatant was collected into an Eppendorf tube. Then the collected solution was evaporated under a stream of nitrogen at 40 ^{o}C using a water bath. The same procedure was repeated two times with 1 mL of ethyl acetate. The residue was dissolved in 100.0 µL of methanol and was injected to HPLC.

A mixture of methanol : acetonitrile : 2% acetic acid in water (20:25:70 v/v) was used as the mobile phase for all HPLC analyses, as it was found to be the ratio which gave the best resolution (Song *et al*., 2002). The retention time of cinnamic acid was 16 min. The mobile phase was degassed using a sonicator (Sonorox, super

RK 1028 CH, Bandelin Electronics, Berlin) and it was filtered through 0.45µm pore size nylon membrane filter prior to use. The UV detector wavelength was set at 254 nm. First, the HPLC system without the column was washed with the mobile phase for 5 min to remove any air bubbles. Then the column (internal diameter 4.6 mm, particle size 5 µm, length 250 mm) was placed and the system was washed for 20 min prior to the injection of analyte till a stable baseline was observed. Subsequently, the sample was injected manually using 0.025 mL syringe. Cinnamic acid was injected into the HPLC with changing mobile phase solvent ratios. This was done in triplicate, and then the optimum ratio with a greater resolution was selected for further analysis. The plasma series of cinnamic acid (0.5–25 µmol/L) was injected (two injections per sample) into the HPLC after the extraction procedure. Two independently prepared samples were analysed from each concentration.

Statistical Analysis

A calibration plot was drawn, and the minimum level of detection, range, precision, recovery, linear range, and stability of the method were determined. The calibration curves for cinnamic acid were obtained for plasma series.

Limit of detection (LOD)

The LOD was determined using the standard deviation of the regression line and the slope of the calibration curve (cinnamic acid spiked plasma), using standard guidelines for method validation (Q2B Validation of Analytical Procedures: Methodology | FDA, 1996).

Precision, bias/accuracy, repeatability

To investigate precision, bias/accuracy, and repeatability ten independently prepared samples of cinnamic acid (25.0 µmol/L) were extracted and injected into the HPLC. The cinnamic acid concentration was evaluated using the calibration curve, and repeatability, bias, and precision were calculated using standard equations (Q2B Validation of Analytical Procedures: Methodology | FDA, 1996).

Stability

To evaluate stability, plasma samples with cinnamic acid (n = 5) with the concentration of 200 µmol/L were kept at 4 ^{o}C for 5 ds and then analysed using Student's t-test at the 95% confidence level, in order to evaluate the difference in absorbance with the time.

Recovery

In order to study recovery, three independent samples from 3 different concentrations with three replicated analyses were done. The mean absorbance value is given after the extraction was compared to the absorbance of corresponding concentration obtained from a standard cinnamic acid series in methanol.

Pharmacokinetics of cinnamic acid in healthy volunteers

Inclusion criteria

Pharmacokinetic parameters of cinnamic acid in blood were assessed in five healthy volunteers (>18 years). Ethical clearance for the study was obtained from the Ethics Review Committee, Faculty of Medicine, University of Colombo, Sri Lanka (EC/16/099). The participants were between 18 to 60 years, not on any other vitamin or mineral supplementations, having normal hepatic or renal functions, non-lactating, and non-pregnant.

Preparation of cinnamon extract for oral administration

To prepare the cinnamon powder for the study, CZ bark (Kosgoda, Sri Lanka) (3 g) was powdered and it was soaked in boiling water (250 mL) for 10 min in a closed cup. The entire extract along with undissolved parts was administered to volunteers.

Blood sample collection

The participants were asked to come after 10 h of overnight fasting. On the day of the study, initially, a baseline blood sample was taken at 8.00 am (0 h). Subsequently, the content of the above prepared CZ solution was given to study participants to drink. Subsequent blood samples were taken at 5 min, 15 min, 30 min, 60 min, 3 h and 6 hours. A 24-hour sample was taken in the morning of the following day at 8.00 am. Each blood sample was about 2–2.5 mL and was obtained from the ante-cubital fossa under sterile conditions. Subjects were given standard meals during the period of the study and CZ was avoided in the preparation of these meals.

Analysis of samples

The blood samples were separated by centrifugation and the supernatant (plasma) was collected. An aliquot (250.0 µL) plasma sample was acidified with 75.0 µL of 0.1 mol/L HCl and it was vortexed for 1 min. A 25.0 µL portion of methanol was added to it. Then the same extraction procedure was followed as the cinnamic acid in the plasma sample described above. Finally, it was injected into the HPLC and the chromatograms were obtained. Using the calibration curve the plasma cinnamic acid concentrations were calculated. Then the concentration-time curve was drawn for extracted human plasma samples.

Pharmacokinetic parameters

Pharmacokinetic parameters were calculated using the non-compartment extra-vascular model applied for the cinnamic acid plasma disposition curves. The area under the plasma concentration-time curve (AUC) was calculated by the use of the mixed log-linear trapezoidal method. Values for the maximum plasma concentration (C_{max}) and time to peak plasma concentration (T_{max}) were directly determined from the plasma concentration-time curve. The elimination half-life ($T_{½}$ in minutes) was calculated as $0.693/K_e$, in which K_e was the elimination rate constant. Parametric and non-parametric statistical tests were done using SPSS version 14 (SPSS Inc., Chicago, IL, USA). Dichotomous variables are reported as numbers and percentages and compared using chi-square test. Continuous variables are presented as mean (± SD) and intergroup comparisons were conducted with Student's t-test or ANOVA with *post hoc* analysis. In all analyses, a $p < 0.05$ was considered as statistically significant.

RESULTS AND DISCUSSION

Development and validation of HPLC method

The plasma series of cinnamic acid (0.5–200 µmol/L) were injected to HPLC. Within the concentration range, a linear calibration plot was obtained for cinnamic acid. The results of concentrations of 0.5–25 µmol/L are shown in Figure 1.

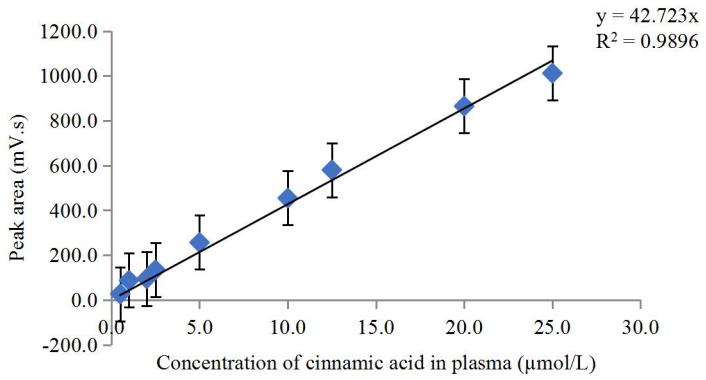

Figure 1: Calibration curve for cinnamic acid in plasma (0.5–25 µmol/L)

Linear range

The linear range was from 0.5–200 µmol/L in cinnamic acid spiked plasma series.

LOD, repeatability, bias, and precision

Repeatability, bias, and precision were evaluated by measuring the absorbance of ten independently prepared plasma samples with cinnamic acid (25.0 µmol/L) after the extraction procedure. The precision/relative standard deviation (RSD) of ten samples was 7.73%. The bias and repeatability of the method were 4.20% and 5.63, respectively. Using the function STEYX in MS-Excel the standard deviation of the regression line was found to be 15.013 and the slope of the line was 44.77. The LOD was 1.11 µmol/L with 10 plasma samples.

Stability

The stability data of the cinnamic acid samples in plasma after 5 days at 4 ^{o}C were evaluated. The mean concentration of two data sets obtained on different days was tested using the two sample *t*-test at 95% confidence level. At 95% confidence level, there was no significant difference between the mean concentration of the two data series. Therefore, it was found the plasma samples with cinnamic acid are stable when stored at 4 ^{o}C up to 5 days. The stability of CA and hippuric acid in rat plasma samples were previously reported as 12 hours at room temperature, 24 hours at 4 ^{o}C and 7 days at -70 ^{o}C (Chen *et al*., 2009).

Recovery

The recovery of the extraction method is 95–125% which indicates the efficiency of the extraction method. According to FDA, the mean recovery should be 100 $\pm$ 2 at each concentration over the range of 80–120% of the target concentration. Therefore the recovery of the method is acceptable and it has been also recorded the recovery of cinnamic acid as 71.5–85.0% in previous studies (Chen *et al*., 2009).

Pharmacokinetics study

The sample size was 5, of which three participants were males. Mean (± SD) age, height, weight and BMI were 26.2 ± 3.0 years, 169.8 ± 8.9 cm, 70.6 ± 12.8 kg and 24.3 ± 2.7 kg/m^2, respectively. The change in mean plasma cinnamic acid concentration (± SD) with time, using time zero as the reference point is shown in Figure 2. Plasma cinnamic acid concentration increased from baseline (0 h) and the maximal concentration achieved in the blood (C_{max}) was 1.9 ± 1.5 µmol/L. The time taken to reach the maximal concentration (T_{max}) was 15 minutes. Subsequently, the concentration gradually decreased (Figure 2). The area under the curve (AUC) from time of administration to the time of last observation was 588 µmol - min/L. The elimination rate constant (K_e) was 0.019 min^{-1}. The elimination half-life ($T_{½}$) was 36 minutes.

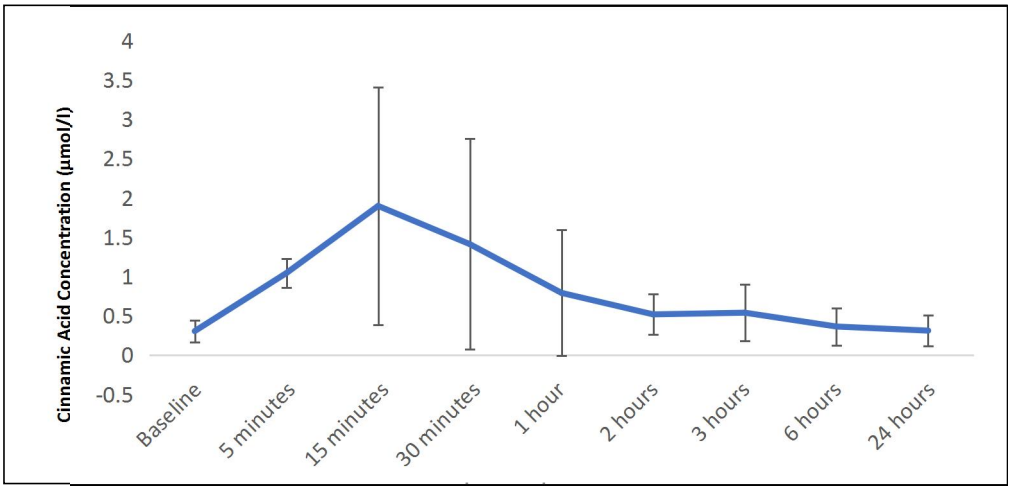

Figure 2: Change in mean cinnamic acid concentration (± SD) with time

The present study is the first to describe a sensitive, specific, and rapid HPLC method with UV detection for the determination of metabolites (cinnamic acid) of *Cinnamomum zeylanicum* in human plasma. Our results show that this validated method is suitable for pharmacokinetic studies of *Cinnamomum zeylanicum* in humans, with advanced HPLC using high sensitivity detectors. These findings will help further studies on *Cinnamomum zeylanicum*, which is now emerging as a potential pharmaceutical agent for the treatment of several diseases, including diabetes, hyperlipidaemia, hypertension, cardiovascular disease and Alzheimer's disease (Ranasinghe *et al*., 2013) Obtaining human pharmacokinetic information is an essential step in the new drug development process, which helps to ensure the appropriate usage of medicines. The current method will be effective in detecting metabolites of cinnamon in plasma. Furthermore, identification of metabolites of *Cinnamomum zeylanicum* detectable in human plasma would help in the identification of active compounds responsible for the observed pharmacodynamic properties.

The metabolites of *Cinnamomum zeylanicum* identified for the purpose of the present study were cinnamaldehyde, benzoic acid, and cinnamic acid, based on evidence from previous animal studies (Yuan *et al*., 1992; Song *et al*., 2002; Chen *et al*., 2009). However, at the initial screening, cinnamaldehyde was excluded from further analysis due to the tailing nature of the peak irrespective of the concentration. Furthermore, only cinnamic acid was identified to be present in the blood after oral administration of *Cinnamomum zeylanicum* in humans. The standards used in the present study were prepared in methanol due to the higher solubility of these compounds in methanol than in water. The developed method was linear for cinnamic acid in the plasma matrix from 0.5–200.0 µmol/L. Chen *et al*. (2009) have recorded a linear range of 0.34–33.78 µmol/L in rat plasma. The linear range of cinnamic acid will permit the use of this method for future pharmacokinetic studies. Furthermore, the method was specific for cinnamic acid and the precision/relative standard deviation (RSD), bias, and repeatability of the method were 7.73%, 4.20% and 5.63 respectively. The sample was stable up to five days at 4 ^{o}C. The recovery of the method was 95–125% and the LOD was 1.11 µmol/L. All these validation parameters are in satisfactory levels. According to Song *et al*. (2002) within day precision was approximately 3.7–9.3% and day to day precision was 2.4–5.8% in animal studies.

As per the results, the maximal concentration reached in plasma (C_{max}) was 1.9 ± 1.5 µmol/L. The time taken to reach maximum plasma concentration (T_{max}) and elimination half-life ($T_{½}$) of cinnamic acid in humans was 15 minutes and 36 minutes, respectively. In animal studies involving Sprague-Dawley rats with *Cinnamomum cassia*, the T_{max} and $T_{½}$ of cinnamic acid was 7 ± 6 minutes and 20 ± 7 minutes respectively after intragastric administration (Chen *et al*., 2009). Li *et at*. (2008) reported that the plasma concentration of cinnamic acid (from *Cinnamomum zeylanicum*) reached the maximum at 1.8 hours and the $T_{½}$ was 3.1 hours after intragastric administration in rabbits while Yang *et al*. (1994) reported a T_{max} of 53 minutes and a $T_{½}$ of 5.7 hours after intragastric administration of Baoxin pill (a pill containing *Cinnamomum cassia* and several other herbal ingredients) in rats. The observed differences are likely due to differences in cinnamon species used (*Cinnamomum cassia* or *Cinnamomum zeylanicum*), animal species tested (rats, rabbits, or humans), dosage forms utilized (powder or capsules) or the composition of the dosage form (cinnamon only or cinnamon mixed with other ingredients). Hence, further studies are required to replicate these findings from this first study using Ceylon cinnamon in healthy humans and conclusively determine the pharmacokinetic parameters of cinnamic acid after oral administration of *Cinnamomum zeylanicum* in humans.

CONCLUSION

In conclusion, the present study developed a sensitive and specific HPLC method to detect cinnamic acid, a key metabolite of *Cinnamomum zeylanicum* in humans. This method is suitable for pharmacokinetic studies of *Cinnamomum zeylanicum* in humans. The study also determined the maximal concentration reached in plasma (C_{max}), time taken to reach maximum concentration (T_{max}) and elimination half-life ($T_{½}$) of cinnamic acid in humans. The identified pharmacokinetic parameters (C_{max}, T_{max}, and $T_{½}$) would help in the further development of CZ as a pharmaceutical agent for use in humans.

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