Pharmacokinetics of xanthohumol in rats of both sexes after oral and intravenous administration of pure xanthohumol and prenylflavonoid extract

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Abstract

Background. Female inflorescences of hops (Humulus lupulus L.) are wildly used in the brewing industry. Hops have been also used for ages in folk medicine. Xanthohumol (XN) is a most abundant prenylated flavonoid present in hops.

Objectives. To determine pharmacokinetic parameters and bioavailability of pure XN and XN given in prenylflavonoid extract obtained from spent hops (HOP).

Material and methods. Fifty-six Wistar rats (28 females and 28 males) were administered with XN or HOP. Xanthohumol was administered either intravenously (iv.) (10 mg/kg) or orally (per os (p.o.)) (40, 100 and 200 mg/kg). Extract obtained from spent hops was administered p.o. and its doses were based on XN content (doses were equivalent to XN dose of 40, 100 and 200 mg/kg, respectively). After administration of XN or HOP serum, XN concentration was measured at different time points (0, 0.25, 0.5, 1, 2, 4, 6, 12, 24, 48, 72, and 96 h). Non-compartmental analysis was used to assess the pharmacokinetics (PK) of XN in rats.

Results. The XN PK in rats after intravenous administration is characterized by extensive distribution followed by delayed elimination from the body. Enterohepatic recirculation is likely to play a role in XN PK. Some fraction of the orally administered XN reaches central compartment rapidly; however, the overall absorption is very limited and probably saturable. The formulation-dependent factors also play an important role in the bioavailability of the drug. Although the CMAX concentration was higher in female rats receiving XN orally comparing to males, the other pharmacokinetic parameters were unaffected by the rats’ sex.

Conclusions. The same doses of XN may be administered to male and female subjects, as its pharmacokinetics is not affected by sex.

Key words: bioavailability, pharmacokinetics, prenylflavonoid, rat, xanthohumol
Introduction

Female inflorescences of hops (Humulus lupulus L.) are widely used in the brewing industry to preserve beer and to give beer aroma and flavor. Apart from being used in the brewing industry, hops have been used for ages in folk medicine. In traditional medicine, hops are used mainly to treat sleep disturbances. However, they are also used as stomachic, antibacterial and antifungal remedy. They have also been known to be estrogenic, and herbal remedies containing hops are used to alleviate menopausal symptoms. Prenylated flavonoids belong to substances present in hops that contribute to their bioactivity, and xanthohumol (XN, Fig. 1) is the most abundant prenylated flavonoid present in hops.

Very few studies have been published on pharmacokinetics of XN and hop prenylflavonoids. On the one hand, reported studies investigated low doses of XN (1–17 mg/kg orally, 1.86 mg/kg intravenously (iv.)) and only male rats were used in these studies. On the other hand, toxicological studies revealed that very high doses of XN are safe. The dose of 500 mg/kg induced no toxic effects and the dose of 1000 mg/kg was associated only with mild hepatotoxicity. Taking these facts into account, we decided to investigate the pharmacokinetics of higher doses of XN and to investigate rats of both sexes. Additionally, we decided to compare pharmacokinetics of 2 formulations of XN (pure XN and HOP) to evaluate whether compounds in extracts, mainly other prenylflavonoids, present in the extract affect the bioavailability of XN and its pharmacokinetics.

The aim of the present study was to compare the pharmacokinetic (PK) parameters of XN and prenylflavonoid extract in Wistar rats of both sexes, and to determine the influence of sex on the pharmacokinetics of XN. A single dose pharmacokinetic study was conducted at 3 oral (per os (p.o.)) dose levels and 1 iv. dose level in order to determine the bioavailability of XN and dependence of pharmacokinetic parameters on dose level, formulation (pure XN or HOP) and sex.

Material and methods

Plant materials and samples preparation of prenylflavonoid extract and xanthohumol

Xanthohumol and HOP used in animal studies were obtained from brewing industry waste – spent hops (Fig. 2). Spent hops were obtained from production of hop extracts (New Chemical Syntheses Institute, Puławy, Poland) by supercritical carbon dioxide extraction of hops Humulus lupulus cv. Magnum collected in 2015 in Lublin region (SE, Poland).

Prenylflavonoid extract was obtained as a result of semi-industrial and laboratory process. The first stage of production started at Wrocław Technology Park (Poland), where 92 kg of spent hops were added to 0.8 m³ of acetone (POCH, Gliwice, Poland) in the batch reactor (2 m³) for 2 h with continuous stirring (120 rpm). The pulp formed was stirred for another 2 h at 30°C, left for sedimentation, and acetone fraction was pumped through a cotton bag filter (0.1 mm mesh) to vacuum-evaporatory module and the extract was concentrated.
under vacuum at 40°C to a volume of about 40 L, stored in a high-density polyethylene (HDPE) industrial barrel closed under nitrogen atmosphere at room temperature and used directly in further laboratory purification steps. Half a liter of the extract was concentrated with a rotary-evaporator to volume, at which the beginning of precipitation was observed, typically to about 80 mL; then 100 mL of ice cold 1M NaOH was added, followed by 400 mL of cold distilled water. The slurry obtained was centrifuged for 4 min at 3000 × g and the resulting supernatant was collected and acidified with ice-cold 1M HCl. A new precipitate was formed, collected, washed with cold distilled water, air dried and stored at −20°C. The precipitates (prenylflavonoid extract – HOP) consisting mainly XN (121 mg/g dry weight), isoxanthohumol (IXN), 41 mg/g dry weight) and polyphenol fraction were pooled, air dried, ground and further used directly in animal studies or in the purification of XN.

Portions, 5–6 g, of precipitate were dissolved in 30 mL of MeOH (POCH) and purified on column chromatography with Sephadex LH 20 (GE Healthcare, Chicago, USA) and methanol as a mobile phase. Fractions were analyzed by TLC (Merck Silica Gel 60, F254, 0.2 mm, eluent: chloroform: methanol (9:1 v/v)) and fractions containing only XN were collected, evaporated and used after additional air drying in animal studies (>98% purity by HPLC/NMR).

6-prenylnaringenin (6PN), xanthohumol B (XN B) and xanthohumol D (XN D) standards were obtained as by-products during the purification of XN (results not shown). Xanthohumol C (XN C) was obtained by chemical oxidative cyclisation, iso-xanthohumol (IXN) by chemical isomerization of XN\textsuperscript{7} and 8PN was obtained by chemical demethylation of XN\textsuperscript{8}.

The XN content in XN batches and HOP was evaluated by HPLC on a Dionex Ultimate 3000 instrument (Thermo Fisher Scientific, Waltham, USA) with a diode array detector (detection at 360 nm wavelength) using the analytical HPLC column Agilent ZORBAX Eclipse XDB (Agilent, Santa Clara, USA) 5 μm (4.6 × 250 mm). Elution was carried out with a gradient of 40% to 100% of solvent B (1% formic acid in MeCN) in solvent A (aqueous 1% formic acid) in 15 min at the flow rate of 0.8 mL/min after the initial 2 min at 40% solvent B, then from 100% to 40% of solvent B over the course of 7 min and held for 2 min in 40% of solvent B. Isoxanthohumol content in HOP was evaluated with the same method, but detection was carried at 290 nm (Fig. 3). NMR spectra (1H-NMR) were recorded on a DRX Avance\textsuperscript{10} 600 (600 MHz) instrument (Bruker, Billerica, USA) in acetone-d\textsubscript{6} (Fig. 4).

**Animal study**

The study was conducted on 56 12-week-old Wistar rats (28 males and 28 females, weighing 208.2 ±17.3 g) that were housed under standard conditions of temperature (21–23°C), humidity (60–70%), and a light-dark cycle (12:12 h). Animals were fed with a standard diet (LSM, Agropol, Motycz, Poland). Access to food and water was ad libitum and was monitored once daily.

Acclimated animals were randomized into 7 groups of 8 animals each (4 females and 4 males) receiving either XN or HOP: XN was administered either iv. (group XN-IV: 10 mg/kg), or p.o. (groups XN-L, XN-M and XN-H receiving 40, 100 and 200 mg/kg, respectively). Extract obtained from hops was administered p.o. and its doses were based on XN content (groups HOP-L, HOP-M and HOP-H received the extract at doses equivalent to XN dose of 40, 100 and 200 mg/kg, respectively).

For each oral dose level, appropriate amounts of XN powder or HOP were dissolved in dimethyl sulfoxide (DMSO) (Sigma-Aldrich, Darmstadt, Germany) (1 g of XN in 1 mL of DMSO) and then diluted in 0.9% saline solution. Animals received a single oral dose by gavage (40, 100 or 200 mg/kg in 2 mL solution/kg). The animals in the XN-IV group were given an iv. injection (10 mg/kg in 2 mL solution/kg) of XN dissolved in DMSO (1 g of XN in 1 mL of DMSO and diluted in 0.9% saline solution). Blood samples (0.3 mL) were obtained via catheter from the tail vein of each rat at the following time points: 0, 0.25, 0.5, 1, 2, 4, 6, 12, 24, 48, 72, and 96 h. After each blood draw, 0.3 mL of 0.9% saline solution was injected iv. and the catheter was flushed with heparinized saline (20 U/mL). Blood samples were placed in collection tubes coated with heparin and stored on ice immediately after collection. Samples were stored at −80°C until analysis for XN.

Study protocol was approved by the First Local Ethic Committee for Animal Experiments in Wroclaw, Poland, and animal experiments were therefore performed in accordance with ARRIVE guidelines and were carried out in accordance with EU Directive 2010/63/EU for animal experiments.

**Sample preparation**

Sample preparation procedure has been adapted from Legetto et al.\textsuperscript{4} with minor modifications. Aliquots of 50 μL of whole blood in duplicate were diluted with sodium acetate buffer (0.1M, pH 4.7), spiked with naringenin (NAR) (12.6 ng in 2-propanol) (Sigma-Aldrich,) as the internal standard, and treated with 600 U of *Helix pomatia* hydrolysates dissolved in sodium acetate buffer (Sigma-Aldrich) for 3 h at 37°C in a total volume of 600 μL to convert conjugates (glucuronides and sulfates) into their free aglycone forms. After incubation, solutions were extracted thrice with diethyl ether (1 mL) and centrifuged for 1 min at 8500 g. The combined ether extracts were dried under a stream of nitrogen. The residues were dissolved in 0.1 mL of 0.1% formic acid solution in methanol, briefly vortexed, sonicated and analyzed directly by (LC-MS/MS).

Calibration curves were prepared by spiking blank rat whole blood with known concentrations of flavonoids...
and the internal standard, (NAR), using 16 concentration levels covering the entire concentration range for all analytes in the samples. The whole blood calibration samples were treated the same as the samples obtained from dosed animals. Limit of quantitation (LOQ) represents the lowest concentration in a sample that can be determined with acceptable precision and accuracy (S/N > 10), whereas limit of detection (LOD) represents the lowest concentration in a sample that can be detected (S/N > 3).

Fig. 3. HPLC chromatograms of HOP at 360 nm (left) and 290 nm (right)
**LC-MS/MS analysis**

Liquid chromatography–mass spectrometry (LC-MS/MS) was performed on an Agilent 6400 triple quadrupole instrument (Agilent) operated at a source temperature of 350°C with a needle voltage of 4500 kV. Nitrogen was used as the source gas, curtain gas, and collision gas. Selected reaction monitoring (SRM) experiments were conducted at collision energies ranging from 25 to 40 eV. Concentrations were calculated using the internal standard calibration method.

The Agilent 1200 HPLC system (Agilent) was used in this study. Chromatographic separations of prenylflavonoids were achieved on a 2.6 μm Accucore C8 column 150 × 3 mm (Thermo Fisher Scientific) eluted in a gradient from 25% to 60% solvent B (0.1% formic acid in ACN) in solvent A (aqueous 0.1% formic acid) over 8.5 min at a flow rate of 0.5 mL/min after an initial 2.0 min at 25% solvent B, then from 60% B to 100% B over 1.0 min. The column was washed with 100% solvent B for 2.0 min and re-equilibrated at 25% solvent B for 7 min prior to each injection. Precursor-product ion transitions for SRM were developed using standards. Selected reaction monitoring transitions used for quantitation included: [M]–353-119 for XN and [M]–271-119 for NAR.

**Pharmacokinetic analysis**

Non-compartmental analysis was used to assess the pharmacokinetics (PK) of XN in rats (TP4.1 software; ThothPro, Gdańsk, Poland).

The following parameters were determined for iv. administration: the area under the concentration–time curve from time 0 to the last sampling (AUC⁰→ₜ), the area under first moment curve from time 0 to the last sampling (AUMC⁰→ₜ), mean residence time (MRT⁰→ₜ), initial concentration (C₀), relative body clearance (ClB), relative apparent volume of distribution at steady state (Vdss), elimination half-life (T₁/₂el), and biological half-life (T₁/₂). The areas were calculated by the trapezoidal rule. For the determination of T₁/₂el, at least 3 last datapoints from the linear portion of the terminal slope were used. The T₁/₂ was calculated as follows:

\[ T_{1/2} = MRT_{0→t} \times 0.693. \]

For the oral study, AUC⁰→ₜ, AUMC⁰→ₜ, MRT⁰→ₜ, T₁/₂el, T₁/₂, as well as the peak concentration (Cmax) and the time when it was observed (Tmax) were assessed. Mean absorption time (MAT) after oral administration was calculated as follows: MAT = mean MRTp.o. – mean MRTv. The bioavailability (F) of orally administered XN was
calculated by comparing the AUCs of XN after p.o. and iv. administration according to the following formula:

\[ F(\%) = \frac{\text{mean AUC}_{0→t} \times \text{dose i.v.}}{\text{mean AUC}_{0→t} \times \text{dose p.o.}} \times 100\% \]

Since numerous samples were found to contain very low and variable concentrations of XN, data below the limit of quantification (BLOQ) was not ignored but included calculations based on the method by Hornung and Reed. All values appearing in the early part of the concentration–time curve were substituted by the value of LOQ/2 and treated as a real value. In the elimination phase, the first BLOQ value was substituted with LOQ/2 and the following BLOQ values were ignored.

**Statistical analysis**

The distribution of PK parameters was assessed by the Shapiro–Wilks test. Almost all parameters were characterized by normal distribution and were therefore compared with Student’s t-test between groups. Only \(T_{\text{max}}\) lacked normal distribution and was compared using the Mann–Whitney U test. Statistical analysis was carried out by means of STATISTICA v. 13 (Tibco Software Inc., Palo Alto, USA) and Excel (Microsoft Corp., Redmond, USA).

**Results**

Good linear relationship was obtained in the concentration range of 4.5–4500 µg/L \((y = 0.0005x + 0.0003, R^2 = 0.9997)\) of XN in whole blood. The LOQ and LOD for XN in the whole blood were 2.5 µg/L and 0.4 µg/L, respectively.

Figure 3A depicts the mean serum concentration-time profile of XN. The pharmacokinetic parameters are listed in Table 1. The elimination half-life of XN was 173.9 h and the half-life was 7.7 h.

The serum profile of XN after oral administration is shown in Fig. 3B for pure XN and in Fig. 3C for XN given in HOP. Pharmacokinetic parameters are listed in Table 1, showing the bioavailability of pure XN ranging from 0.96% to 1.16% and lower. After oral administration of pure XN (40, 100 and 200 mg/kg) and HOP in a dose equivalent for XN 200 mg/kg, XN was detectable up to 96 h, whereas after oral administration of HOP in doses equivalent for XN 40 and 100 mg/kg no XN was detected after 72 h. The AUC\(_{0→t}\) of XN was 7.7 times and 5.0 times higher for pure XN than for HOP for doses of 100 and 200 mg/kg, respectively. The \(C_{\text{MAX}}\) of XN was 2.3 times, 8.4 times and 11.7 times higher for pure XN than for HOP for doses of 40, 100 and 200 mg/kg, respectively.

Table 2 summarizes the influence of sex on XN pharmacokinetics. \(C_{\text{MAX}}\) was higher 1.7 times and 1.8 times in females than in males receiving XN in doses of 100 and 200 mg/kg, respectively.

**Discussion**

The concentration-time curve and the PK parameters for the intravenous administration are shown in Fig. 3A and Tables 1 and 2, respectively. As can be appreciated from Fig. 3A, a relatively long distribution phase (lasting about...
10 h) is followed by an even longer and flat elimination. In some individuals (particularly males), concentrations in the elimination phase even exceed the concentrations at the end of the distribution phase. A similar rise in XN concentration after iv. administration of XN to rats has been reported by Legette et al., who have suggested enterohepatic recirculation as the underlying mechanism. Enterohepatic recirculation of hop prenylated phenols suggest also observation reported by Rad et al. As can be seen in Table 2, no statistically significant differences between sexes have been found for iv. administration. Although there was a tendency of higher internal exposure (as expressed by AUCIV) in females, high interindividual variability in this group and small number of animals preclude any firm conclusions. A relatively long MRT does not differ much between males and females. Volume of distribution is high and may suggest deep penetration into tissue(s). Although Clh is slightly higher in males, the T1/2 estimates are also higher in this group suggesting somewhat slower elimination in males. The latter parameter, however, should be interpreted with caution as it may be biased by the aforementioned enterohepatic recirculation. The T1/2, which is less affected by the lack of linearity in the elimination phase, does not confirm any sex-related difference in XN elimination. The initial concentrations were somewhat higher in males but, again, high interindividual variability precludes firm conclusions.

Studies using the Caco-2 human intestinal epithelial model indicate that hop prenylated flavonoids are absorbed at a slow to moderate rate through the intestinal epithelium. XN accumulates in intestinal epithelial cells and then are gradually released to the general circulation, while 8PN crosses the intestinal epithelium via passive diffusion. Tables 1 and 2 summarize the PK of XN administered orally at the dose of 40 mg/kg. Due to very low XN concentrations observed after administration of the HOP-L formulation, only the CMAX and the corresponding TMAX could be assessed. In the case of XN-L formulation, the CMAX was significantly higher as compared to HOP-L, and all PK phases could have been observed (Fig. 3B,C). Steep increase in blood XN followed by a pointed peak of CMAX may suggest zero-order absorption. Similar to the iv. administration, the distribution phase is followed by a flat and long elimination phase. No sex-dependent differences were observed in the PK parameters. A low AUC translated into low bioavailability of about 1%. Longer MRT values, as compared to iv. administration, resulted in very long MAT, particularly in females. Such a long MAT value could suggest a flip-flop phenomenon where the prolonged absorption is a limiting factor for the elimination. However, this is not the case in the present study, as the absorption seems to be fast and there is no difference in the slope of the elimination phase between the intravenous and the oral studies (as seen in the T1/2). Therefore, the current MAT estimations seem to be biased by the very low bioavailability of the oral formulations on the one hand, and slow elimination of the absorbed fraction of the drug on the other.

The administration of XN at the dose of 100 mg/kg in the formulation XN-M resulted in the proportional increase in the AUC without any visible effect on the absorption phase as seen in the lack of change in the MRT and MAT (Tables 1 and 2). This questions the possibility of zero-order absorption suggested by the shape of the curve in both XN-L and XN-M groups. The CMAX

### Table 2. The influence of sex on pharmacokinetic parameters (mean ±SD) of xanthohumol after single intravenous or oral administration of pure xanthohumol to rats of both sexes (n = 4/group)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Units</th>
<th>IV</th>
<th>Oral</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>males</td>
<td>females</td>
</tr>
<tr>
<td>AUCIV-IV</td>
<td>mg*h/  L</td>
<td>10.41 ±2.96</td>
<td>16.79 ±6.04</td>
</tr>
<tr>
<td>AUMCIV-IV</td>
<td>mg<em>h</em>/L</td>
<td>78.64 ±40.06</td>
<td>109.26 ±33.59</td>
</tr>
<tr>
<td>MRTIV</td>
<td>h</td>
<td>7.12 ±1.85</td>
<td>8.70 ±6.72</td>
</tr>
<tr>
<td>MAT</td>
<td>h</td>
<td>–</td>
<td>1.50 ±2.96</td>
</tr>
<tr>
<td>CMAX</td>
<td>µg/L</td>
<td>11329 ±4733</td>
<td>6792 ±2930</td>
</tr>
<tr>
<td>TMAX</td>
<td>h</td>
<td>–</td>
<td>–</td>
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<tr>
<td>F</td>
<td>%</td>
<td>–</td>
<td>1.01</td>
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IV – intravenous; AUCI-IV – area under the curve; AUMCIV-IV – area under the first moment curve; MRTIV – mean residence time; MAT – mean absorption time; Clh – relative body clearance; Vdss-rel – relative volume of distribution at steady state; T1/2IV – elimination half-life; T1/2 – half-life; CMAX – peak plasma concentration; TMAX – time to reach peak plasma concentration; F – absolute oral bioavailability.

* p < 0.05 as compared to males receiving the same dose of xanthohumol.
was much higher in XN-M group, particularly in females, but the $T_{\text{max}}$ was similarly short. Both half-lives were similar to the XN-L group, indicating no significant change in the elimination of the compound. In rats treated with the HOP-M formulation, the AUC was more than 7 times lower as compared to the rats administered with XN-M (Table 1). Moreover, very low values (below LOQ) in 3 out of 4 females precluded PK analysis in these individuals. The MRT was significantly shorter and the mean $C_{\text{MAX}}$ was about 9 times lower. The mean bioavailability of 0.13% should be considered extremely low. In the HOP-M group, it was not possible to calculate $T_{1/2\text{el}}$ due to the lack of linearity in the elimination phase.

The saturation of XN absorption was much more visible in the PK of XN after the administration of the highest dose – 200 mg/kg (Tables 1 and 2). In the XN-H group, the mean AUC increased only very slightly as compared to the lower dose (XN-M), which translated into a drop in bioavailability (0.53%). Although the MRT, MAT and $T_{1/2}$ were not changed, the lack of linearity in the elimination phase ($T_{1/2\text{el}}$ impossible to calculate in 5 out of 8 individuals) may suggest limited/prolonged absorption. $C_{\text{MAX}}$, however, was proportionally higher as compared to the XN-M group. In the case of the HOP-L group, the saturated absorption is also seen in the less than proportional increase in the AUC and the drop in the bioavailability (as compared to HOP-M). The mean $C_{\text{MAX}}$ is only slightly higher, and MAT, $T_{\text{MAX}}$ as well as $T_{1/2}$, are prolonged. The concentration-time curve for this group lacks linear elimination and the presence of a secondary peak at 24 h further supports the presence of prolonged/disturbed absorption.

The lower bioavailability of HOP at every dosage level in comparison to similar dosage of pure XN is definitively associated with the complex composition of the prenylflavonoid extract. Despite the undertaken procedure of HOP preparation being highly selective for polyphenol fraction, the complete composition of the HOP cannot be determined. On the basis of the combined data from the HOP $^1$H NMR spectra (Fig. 4, especially the aromatic part 8.0–6.0 ppm) and HPLC analysis (Fig. 3), a rough estimation of total prenylflavonoid content in HOP would be about 30–35%, with XN and IXN being the most abundant. Therefore, it cannot be even speculated whether the complex matrix or other prenylflavonoids affects the bioavailability of XN from HOP.

**Conclusions**

It is concluded that the XN PK in rats after intravenous administration is characterized by extensive distribution followed by delayed elimination from the body. Enterohepatic recirculation is likely to play a role in XN PK. Some fraction of the orally administered XN reaches the central compartment rapidly; however, the overall absorption is very limited and probably saturable. The formulation-dependent factors also play an important role in the bioavailability of the drug. Although the $C_{\text{MAX}}$ concentration was higher in females receiving XN orally compared to males, the other pharmacokinetic parameters were unaffected by rats’ sex. Therefore, the same doses of XN may be administered to males and females.

![Fig. 5. Concentration-time profiles of xanthohumol in rat plasma following (A) intravenous injection (XN IV) of 10 mg/kg, (B) oral administration of pure xanthohumol (XN PO): 40 mg/kg, 100 mg/kg and 200 mg/kg, and (C) oral administration of prenylflavonoid extract (HOP PO): 40 mg XN/kg, 100 mg XN/kg and 200 mg XN/kg. Data is expressed as mean from 8 rats.](image-url)
References


