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Pharmacokinetics of deguelin, a cancer chemopreventive agent in rats

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Abstract *Purpose*: To study the pharmacokinetics of deguelin, a naturally occurring potential cancer chemopreventive agent, in rats. *Methods*: [^{3}H]Deguelin was administered intravenously (i.v.) under anesthesia, and blood samples were collected over 24 h. [^{3}H]Deguelin and metabolites were extracted from plasma with ethyl acetate, and quantified by HPLC. Data were analyzed with the WinNolin pharmacokinetic software package to determine pharmacokinetic parameters. A three-compartment first-order elimination model was used to fit the plasma concentration-time curve. In addition, deguelin concentrations in tissues after i.v. and intragastric (i.g.) administration were determined by HPLC, and excretion (feces and urine) was evaluated over a 5-day period after i.g. administration. *Results*: Deguelin exhibited a mean residence time (MRT) of 6.98 h and terminal half-life ($t_{1/2(\gamma)}$) of 9.26 h. The area under the curve (AUC) and total clearance (Cl) were 57.3 ng · h/ml and 4.37 l/h per kg, respectively, with an apparent volume of distribution (V) and volume of distribution at steady-state (Vss) of 3.421 l/kg and 30.46 l/kg, respectively. Following i.v. administration, the relative levels of tissue distribution were as follows: heart > fat > mammary gland > colon > liver > kidney > brain > lung. Following i.g. administration, the relative levels of tissue distribution were as follows: perirenal fat > heart > mammary gland > colon > kidney > liver > lung > brain > skin. Within 5 days of i.g. administration, about 58.1% of the [^{3}H]deguelin was eliminated via the feces and 14.4% via the urine. Approximately 1.7% of unchanged deguelin was found in the feces, and 0.4% in the urine. *Conclusions:* An initial pharmacokinetic investigation of deguelin showed that this rotenoid has a relatively long MRT and half-life in plasma in the rat. The compound distributed in the tissues and excreted as metabolites, mainly via the feces.

Key words Cancer chemoprevention · Deguelin · Rotenoid · Pharmacokinetics

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Introduction

Cancer is the second leading cause of death in the United States, being the cause of about one in every four mortalities [1]. Cancer chemoprevention is one of the approaches which could help to minimize the incidence of cancer. This approach involves the use of dietary or chemical agents to impair or retard the formation of neoplastic cells. The preventive effect may be achieved either by blocking neoplastic transformation and/or by inhibiting the progression of transformed cells [2, 3, 4].

At present, the use of cancer chemopreventive agents in human populations has not been extensive, but intervention trials have been initiated with tamoxifen [5] and finasteride (Proscar) [6].

Our group has worked for the discovery and evaluation of plant-derived cancer chemotherapeutic agents [7, 8, 9]. One of the bioactive compounds to emerge from this program is deguelin (Fig. 1), a constituent of the bark of the African plant *Mundulea sericea* (Willd.) A. Chev. (Leguminoseae) [10]. *Mundulea sericea* has been used as both an insecticide and an aphrodisiac [10]. In an initial study, deguelin and three other rotenoid constituents, tephrosin, (−)-13α-hydroxytephrosin, and (−)-13α-hydroxydeguelin, were found to inhibit ornithine decarboxylase (ODC) activity induced by 12-*O*-tetradecanoylphorbol 13-acetate (TPA) in cultured mouse epidermal 308 cancer cells [10]. As has been shown in recent studies, ODC plays an important role in tumor development. It is a key enzyme in cell proliferation, and is overexpressed in cancer [11, 12, 13]. The studies also indicated that inhibition of ODC attenuates the enhancement of intestinal and prostate carcinogenesis and cancer metastasis [11, 12, 14]. Being highly effective in this process, the mode of action was investigated as well as the potential to inhibit preneoplastic lesions induced by 7,12-dimethyl(*a*)benzanthracene (DMBA) using mouse mammary glands in organ culture [15]. Deguelin was highly effective in the mouse two-stage DMBA/TPA skin carcinogenesis model, and in rats, mammary tumors induced by *N*-methylnitrosourea were inhibited in a dose-dependent manner [16]. Regulation of ODC induction appears to be a relevant mechanism of action [17].

Given the demonstrated effectiveness of deguelin as a cancer chemopreventive agent in two animal models, the present study was undertaken to evaluate the pharmacokinetic parameters in Sprague-Dawley rats. While this agent was initially developed as a chemopreventive agent, current studies appear to show that deguelin has potential as a chemotherapeutic agent in melanoma. Deguelin, also currently known to be an inducer of apoptosis, appears to have an inhibitory effect on human melanoma cell lines (MEL-1 and MEL-2) [18]. As reported here, the agent has a relatively long plasma half-life and is distributed in organs throughout the body of the rat. Recently, deguelin has been selected by the National Cancer Institute for in vivo antitumor studies. Further studies are being carried out to establish the efficacy of this agent.

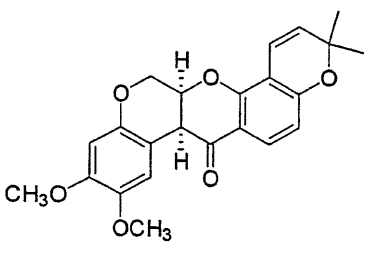

Fig. 1 Structure of deguelin

Materials and methods

Chemicals

Deguelin (97–98% purity, HPLC-UV) was synthesized from rotenone as starting material, essentially by the procedure described by Anzeveno [19]. Cremophor EL and corn oil were purchased from Sigma Chemical Co. (St. Louis, Mo.), ethanol from Midwest Grain Product Co. (Pekin, Ill.), and ethyl acetate and acetonitrile from Fisher Scientific Co. (Fair Lawn, N.J.). Ketamine and xylazine were purchased from Vedco (St. Joseph, Mo.).

Deguelin was dissolved in Cremophor EL solution (Cremophor/ethanol/saline 1:1:6) to yield a 2 mg/ml solution, and was stored in an amber vial. The solution was further diluted with saline to 0.125 mg/ml for intravenous (i.v.) administration, and with corn oil (2 mg/ml) for intragastric (i.g.) administration and tissue distribution studies. [^{3}H]Deguelin was custom-synthesized by SibTech (Elmsford, N.Y.) using a random tritiation procedure, and dissolved in ethanol (0.5 mCi/ml). The specific activity of [^{3}H]deguelin was 20–25 Ci/mmol and the radiochemical purity as determined by TLC was found to be better than 95%. [^{3}H]Deguelin was mixed with deguelin-Cremophor EL solution to obtain deguelin (125 μg/ml) and [^{3}H]deguelin (60 μCi/ml) solutions for i.v. injection. [^{3}H]Deguelin was mixed with deguelin-corn oil solution to obtain deguelin (2.0 mg/ml) and [^{3}H]deguelin (6.5 μCi/ml) solutions for the i.g. excretion studies.

Animals

The research protocols utilized in the present investigation adhered to accepted principles of animal care [20]. Virgin female Sprague-Dawley rats (205–235 g) from Harlan/Sprague-Dawley Laboratories (Indianapolis, Ind.) were used for the study. The animals were received at 10 weeks of age and were randomized by weight for dosing after a quarantine period of 1 week. The animals were fasted overnight and for 2 h after dosing, but were allowed water ad libitum. All animals were housed three to a cage in a windowless room illuminated for 14 h daily at 22 ± 1°C. The basal diet provided to each animal was Prolab RMH 4020 Rat/Mouse Chow (blox; Agway, Syracuse, N.Y.).

Plasma concentration-time curve

Deguelin (deguelin 125 μg/ml and [^{3}H]deguelin 60 μCi/ml) was administered i.v. (2 ml/kg) via the femoral vein under anesthesia using ketamine (50 mg/kg) and xylazine (5 mg/kg). Blood (1.0 ml) was collected via the posterior vena cava at 5, 15, and 30 min, and 1, 2, 4, 8, 16, and 24 h, with three rats at each time-point. Blood samples were placed on ice immediately, centrifuged, and the plasma stored at –20°C for subsequent analysis. Ethyl acetate (4.0 ml) was subsequently added to each sample, which was vortexed for deguelin extraction. The samples were centrifuged after 1 h (1500 *g*) to separate the organic phase from the aqueous phase. Ethyl acetate (3 ml) was removed and dried under nitrogen gas. Acetonitrile (100 μl) was then added to reconstitute the plasma extract solution which was filtered (0.2 μm syringe filter; Whatman, Clifton, N.J.) and 30 μl were analyzed by HPLC. The plasma concentration time-course for deguelin in rats after i.v. administration of 0.25 mg/kg was fitted into a three-compartment first-order elimination model (Fig. 2): $C(t) = A\exp(-\alpha t) + B\exp(-\beta t) + C\exp(-\gamma t)$. Pharmacokinetic parameters were calculated with the WinNonlin pharmacokinetics software package [21].

HPLC analysis

A Waters Corporation (Milford, Mass.) HPLC system consisting of a model 510 pump, a WISP model 712 sample processor, and a model 991 UV photodiode array detector, equipped with Millen-

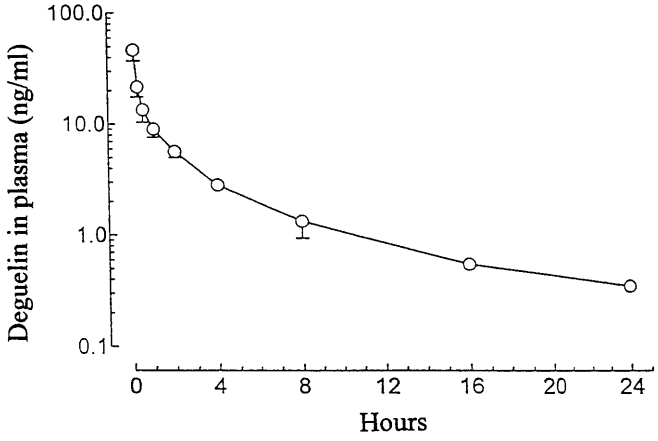

Fig. 2 Plasma concentration-time curve of deguelin after i.v. administration at 0.25 mg/kg with 120 μCi/kg [^{3}H]deguelin in Sprague-Dawley rats. Values are means ± SEM, $n = 3$

nium Chromatography Manager Software version 2.15. A Nova Pak C_{18} column (3.9 × 150 mm) was used.

The mobile phase for HPLC analysis was CH_3CN/H_2O (55:45 v/v). The UV detector was set at 270 nm, and the flow rate was 1 ml/min. The retention time for deguelin was 6.3 min (peak range 6.0–6.7 min).

The eluent representing the [^{3}H]deguelin peak was collected and radioactivity determined by liquid scintillation counting. To determine deguelin recovery, [^{3}H]deguelin (15,000 dpm) was mixed with rat plasma (1.5 ml). A deguelin recovery of 82 ± 1% (mean ± SD, $n = 3$) was established after extraction with ethyl acetate, separation by HPLC, and radioactivity determination.

Tissue distribution

Deguelin (0.25 mg/kg) was administered to rats via the femoral vein under light anesthesia using ketamine (50 mg/kg) and xylazine (5 mg/kg). Three to four animals were killed at 0.08, 0.5, 1, 4, 8, 12, and 24 h after i.v. injection, and at 0.5, 1, 4, 8, 12, 24, and 48 h after i.g. administration (via i.g. needle gavage) and the heart, liver, lungs, kidney, brain, bladder, colon, skin, perirenal fat, and mammary gland were collected. Rats were exsanguinated via the dorsal aorta. Death was assured by opening the thoracic cavity. Tissue samples were weighed and stored at –20°C for subsequent analysis.

A Brinkmann Polytron (PT3000; Kinematica, Littau, Switzerland) was used to homogenize tissue samples in a polypropylene copolymer tube with 3 ml distilled water. The extraction procedure was the same as the procedure for plasma described above. The injection volume for HPLC analysis was 20 μl. A deguelin external standard was used for quantification. Calibration curves were established by plotting the deguelin peak area vs concentration. In carrying out the deguelin tissue recovery procedure, deguelin (0.2 μg) was added to tissue samples from the control animals, then extracted using the previously described methods.

Excretion

The rats were given deguelin (4 mg/kg), mixed with [^{3}H]deguelin (13 μCi/kg) by i.g. administration using an oral gavage needle. Urine and feces samples were collected (four animals per time-point) and measured at 8, 24, 48, 72, 96, and 120 h after i.g. administration. Samples were stored at −20°C for subsequent analysis.

The radioactivity of the urine and feces samples was determined in order to estimate the excretion of deguelin and its metabolites. Each urine sample (0.1 ml) was added to 5 ml scintillation fluid (CytoScint; ICN Biomedicals, Costa Mesa, Calif.) to determine radioactivity using a Beckman LS 5801 scintillation counter. A 100–200-mg aliquot of each feces sample was weighed and 0.2 ml 30% H_2O_2, 0.2 ml formic acid, and three drops of 1-butanol were added to digest the samples. Each feces sample was subsequently placed in a waterbath, and after 120 min at 60°C, 6 ml scintillation fluid was added to each sample for radioactivity determination. The scintillation data were corrected for quenching.

For the quantification of deguelin, 2–4-g samples of feces and 5–10-ml samples of urine were used. Ethyl acetate was used to extract deguelin from feces and urine in an analogous manner to the procedure for plasma and tissues, and samples were analyzed by HPLC. Scintillation data were automatically corrected for quenching by the Beckman Counter.

Results

Plasma concentration-time curve

Pharmacokinetic parameters calculated from data using the WinNonlin pharmacokinetics software package [20] are shown in Table 1. Deguelin (0.25 mg/kg) was administered to rats via the femoral vein under light anesthesia using ketamine (50 mg/kg) and xylazine (5 mg/kg). The plasma time-course of deguelin concentration in rats after i.v. administration of 0.25 mg/kg fitted a three-compartment first-order elimination model (Fig. 2): $C(t) = A\exp(-\alpha t) + B\exp(-\beta t) + C\exp(-\gamma t)$ [20]. Deguelin had a mean residence time (MRT) of 6.98 h and an elimination half-life ($t_{1/2(\gamma)}$) of 9.26 h. The area under the curve (AUC) was 57.3 ng·h/ml, total clearance (Cl) was 4.37 l/h per kg, the apparent volume of distribution (V) of 3.42 l/kg was as reported previously, and the volume of distribution at steady-state (Vss) of 30.5 l/kg was observed.

Tissue distribution

When deguelin (0.2 μg) was added to tissue samples for standard solutions, its recovery (mean ± SD) using this extraction method was found to be 90 ± 5% ($n = 30$) for all tissues. Deguelin concentrations over the 0.5–10 μg/ml range (0.5, 1, 2, 4, 7, and 10 μg/ml) of the standard solutions for the calibration curves exhibited good linearity against each tissue with the areas of their respective absorbance peaks ($r^2 = 0.9996$, $P < 0.0001$). The deguelin samples stored at −20°C were stable for over 1 month.

The concentrations (micrograms per gram wet tissue) of deguelin in rat tissues and organs after i.v. adminis-

Table 1 Pharmacokinetic parameters of deguelin following i.v. administration at 0.25 mg/kg in rats

k10 (h^{-1})	1.27	k12 (h^{-1})	3.84
k13 (h^{-1})	0.74	k21 (h^{-1})	1.80
k31 (h^{-1})	0.12	V ($l \cdot kg^{-1}$)	3.42
$t_{1/2(\alpha)}$ (h)	0.09	$t_{1/2(\beta)}$ (h)	1.25
$t_{1/2(\gamma)}$ (h)	9.25	AUC ($ng \cdot h \cdot ml^{-1}$)	57.26
Cl ($l \cdot h^{-1}kg^{-1}$)	4.36	AUMC ($ng \cdot h^2 \cdot ml^{-1}$)	399.50
MRT (h)	6.97	Vss ($l \cdot kg^{-1}$)	30.46

tration (0.25 mg/kg) are shown in Fig. 3 (heart, kidney, colon, liver brain and lung) and Fig. 4 (perirenal fat and mammary gland). Tissue concentrations followed the order: heart > kidney > colon > liver > brain > lung. There was no detectable concentration of deguelin in the bladder after 24 h, or in the skin after 8 h. The concentration of deguelin in perirenal fat and mammary gland (Fig. 4) increased slowly initially, peaked at 8 h, and then slowly declined over 24 h.

The deguelin distribution was investigated in various organs and tissues after i.g. administration of 4 mg/kg. Figure 5 shows the deguelin distribution in the heart, liver, lung, kidney, brain and colon, while Fig. 6 shows the distribution in perirenal fat, mammary gland and skin. With this administration route, the concentrations followed the order: heart > colon > liver > kidney > brain > lung. Deguelin was undetectable in the bladder. There were similar trends in deguelin distribution in perirenal fat, mammary gland and skin, but perirenal fat had the highest concentration. Deguelin elimination from perirenal fat as well as the mammary gland was slow and remained elevated for 48 h.

Deguelin excretion

The excretion of deguelin and its metabolites was determined by monitoring total radioactivity excreted by the rats. Excretion of [^{3}H]deguelin and its metabolites was mainly via the feces (Fig. 7). Rats excreted approximately 58.1% via the feces and 14.4% of the total dose via the urine within 5 days. The unchanged deguelin recovered from the feces was 1.7% and from the urine was 0.4% of the total dose 5 days after administration. In the urine, the total fraction of the dose partitioning into water was greater than that partitioning into ethyl acetate in the ratio 3.8:1. Deguelin metabolites partitioning into ethyl acetate eluted earlier than the parent compound (deguelin, R_t 6.3 min) as determined by HPLC. Figure 8 shows an HPLC chromatogram for deguelin. In the feces, lipophilic deguelin metabolites were present at higher levels than hydrophilic deguelin metabolites in the ratio 1:0.5. The metabolites were more polar than the parent compound (deguelin).

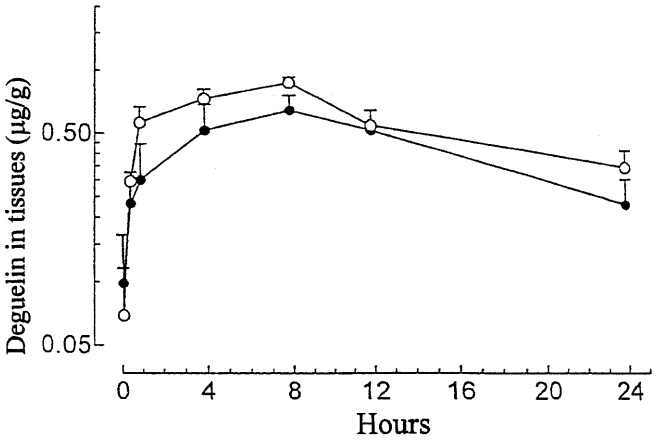

Fig. 4 Tissue distribution of deguelin after i.v. administration at 0.25 mg/kg in perirenal fat (○) and mammary gland (●) in Sprague-Dawley rats. Values are means ± SEM, $n = 3$ or 4

Discussion

Deguelin, a naturally occurring rotenoid, was isolated from the African plant *Mundulea sericea* (Leguminosae)

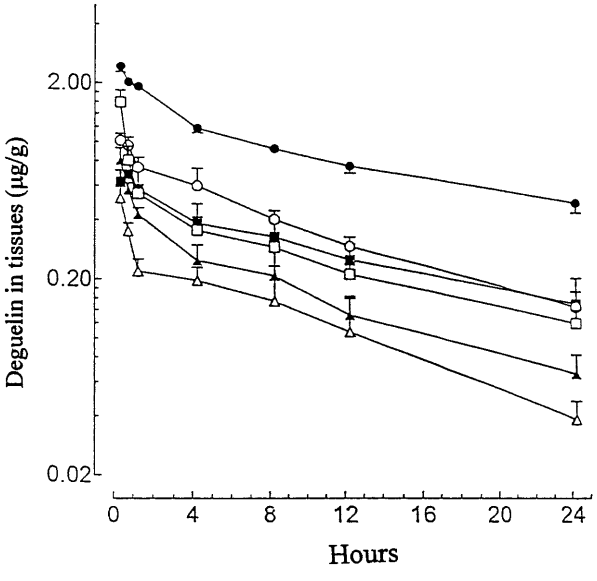

Fig. 3 Organ distribution of deguelin after i.v. administration at 0.25 mg/kg in heart (●), liver (□), lung (△), kidney (○), brain (▲) and colon (■) in Sprague-Dawley rats. Values are means ± SEM, $n = 3$ or 4

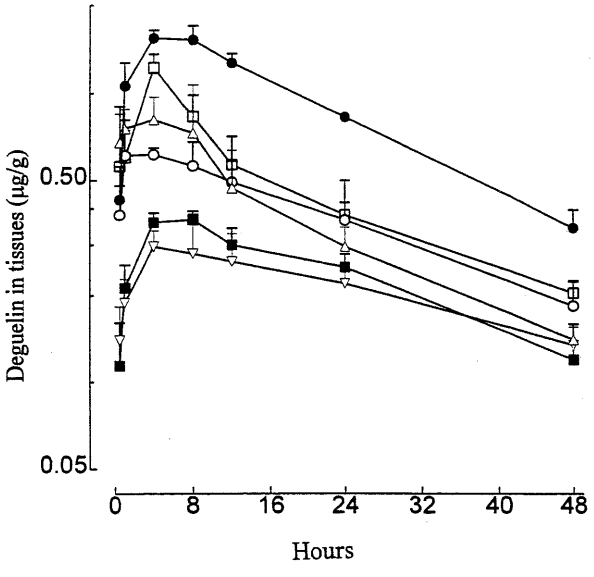

Fig. 5 Tissue distribution of deguelin after i.g. administration at 4.0 mg/kg in heart (●), liver (△), lung (▽), kidney (○), brain (■), and colon (□) in Sprague-Dawley rats. Values are means ± SEM, $n = 3$ to 4

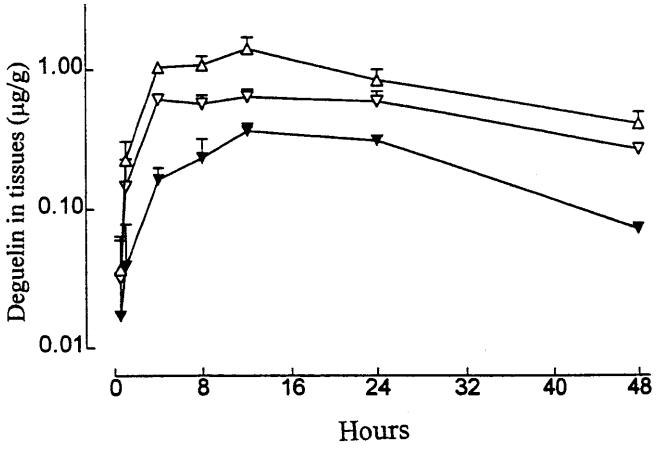

Fig. 6 Tissue distribution of deguelin after i.g. administration at 4.0 mg/kg in perirenal fat (△), mammary gland (▽), and skin (▼) in Sprague-Dawley rats. Values are means ± SEM, $n = 3$ or 4

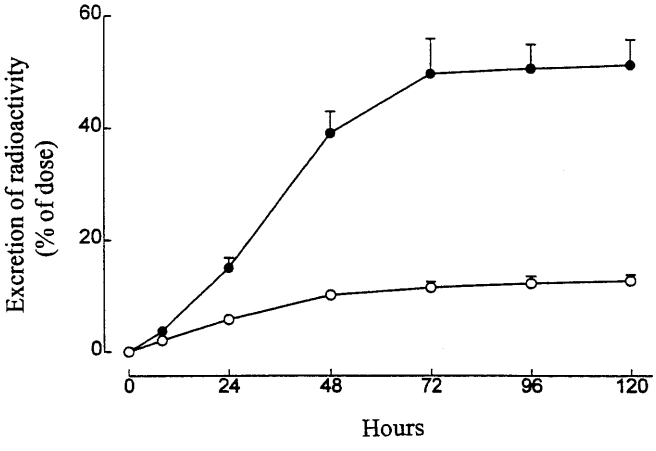

Fig. 7 Excretion of deguelin via feces (●) and urine (○) after i.g. administration at 4.0 mg/kg with 13 μCi/kg [^{3}H]deguelin in Sprague-Dawley rats. Values are means ± SEM, $n = 4$

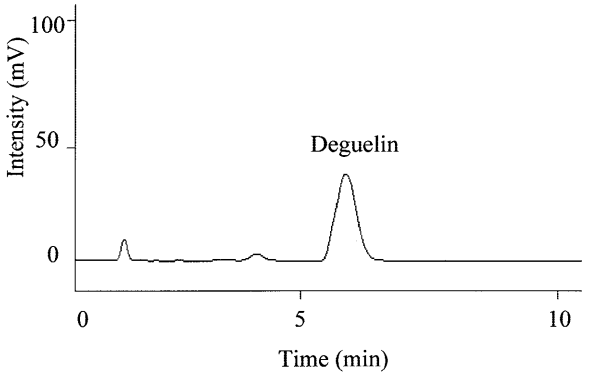

Fig. 8 HPLC chromatogram of deguelin

as a potential cancer chemopreventive agent [8, 9, 10, 15, 16, 17]. Inhibitory effects in skin and mammary carcinogenesis laboratory animal models have been described [16], and one important mechanism appears to be transcriptional regulation of ODC activity [15, 17].

A series of pharmacokinetic studies were carried out in the present investigation. Radiolabeled deguelin administered i.v. (0.25 mg/kg) fitted a three-compartment first-order elimination model. The compound demonstrated a relatively long MRT of 6.98 h and a terminal $t_{1/2}$ of 9.26 h, suggesting that the agent could be administered once daily. Deguelin also exhibited a large volume of distribution (3.42 l/kg) and a large volume of distribution at steady-state (30.5 l/kg).

Deguelin distributed into the heart, kidney, colon, liver, brain, lung, perirenal fat and mammary gland after i.v. administration. The distribution patterns after i.v. administration in perirenal fat and mammary gland differed substantially from that in the other tissues. The Cp_{max} in the perirenal fat and mammary gland occurred within 8 h of administration of the compound. Initial deguelin concentrations (Cp_0) for these tissues ranged from 0.07 to 0.099 μg/g. The initial concentrations in the other tissues (heart, kidney, colon, brain, and lung) ranged from 0.45 (lung) to 0.90 μg/g (heart). The highest concentrations of deguelin in these tissues were observed immediately after infusion. Following i.g. administration of the compound, the highest concentration was observed in the heart. The t_{max} in most tissues occurred within 6 h (heart, liver, lung, kidney, brain and colon). In other tissues (perirenal fat, mammary gland, and skin), the t_{max} was observed at 12 h following i.g. administration.

The excretion of deguelin was mainly via the feces, which accounted for approximately 58.1% of the elimination of the compound, compared with 14.4% via the urine. The fraction of unchanged deguelin excreted via the feces was 1.7%, while 0.4% was excreted via the urine. The remainder was considered to be distributed in tissues. The isolation and structural characterization of the metabolites of deguelin are under way.

In the current study, deguelin (0.25 mg/kg) was administered to rats via the femoral vein under light anesthesia using ketamine (50 mg/kg) and xylazine (5 mg/kg). There are very limited data in the literature regarding the biological activity or biopharmaceutical aspects of deguelin. Future work in these areas will provide better information regarding the metabolism of this rotenoid and metabolites. Deguelin has recently been selected by the National Cancer Institute for further evaluation as an antitumor agent. As a result of deguelin's current and potential future applications as a cancer chemopreventive and/or chemotherapeutic agent, further investigation of its pharmacokinetics in various animal models, as well as in humans, is warranted.

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