

**STUDIES OF THE TOXICOLOGICAL POTENTIAL OF CAPSINOIDS
XII:
A Pharmacokinetic Study of Capsinoid-Containing
CH-19 Sweet Extract in Rats**

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ABSTRACT

Pharmacokinetics of the main capsinoid-components of CH-19 Sweet extract (capsiate, dihydrocapsiate and nordihydrocapsiate) were investigated in rats receiving a single gavage dose of extract containing 10 or 100 mg capsinoids/kg. The resultant blood levels of these capsinoids and a capsinoid-metabolite, vanillyl alcohol, were measured in portal vein and abdominal aorta blood. Capsinoids were never detected. Portal compartment vanillyl alcohol concentrations and AUC increased in direct relationship to dose while the time to maximum concentration of vanillyl alcohol was independent of dose (30 minutes post-dosing) suggesting precipitation in the stomach or intestines was unlikely. Vanillyl alcohol levels were just barely detectable in systemic plasma (5 minutes post-dosing). Significant levels of vanillyl alcohol conjugates, sulfate and glucuronide were detected in the systemic blood. In as much as the orally-administered capsinoids were never detected in the portal vein or systemic circulation, these compounds must be broken down (chemically and/or enzymatically) to vanillyl alcohol.

INTRODUCTION

Capsaicin occurs naturally in plants of the *Solanaceae* family and is the compound mainly responsible for the pungency associated with the fruit of red pepper plants (Figure 1). Capsaicin homologues are called capsaicinoids; these compounds consist of acid amides of vanillyl amine and C8 to C13 fatty acids. The major capsaicinoids in pungent red peppers are capsaicin (*[E]*-[4-hydroxy-3-methoxybenzyl]-8-methyl-6-nonenamide), dihydrocapsaicin, the 6, 7-dihydro analogue of capsaicin and nordihydrocapsaicin, the mono-nor homologue of the acyl residue of dihydrocapsaicin⁸ (Figure 1). Recently, ‘novel’ capsaicinoid-like substances were found in the fruit of CH-19 Sweet, a non-pungent cultivar of *Capsicum annuum* L.²¹ Previous work by Kobata and others^{9,10} determined the structures and named these substances capsiate (4-hydroxy-3-methoxybenzyl *[E]*-8-methyl-6-nonenoate, Figure 2), dihydrocapsiate (4-hydroxy-3-methoxybenzyl 8-methyloctanoate, DHC), and nordihydrocapsiate (4-hydroxy-3-methoxybenzyl 7-methyloctanoate), respectively. These compounds have an ester bond replacing the amide bond found in capsaicinoids (ie, between the vanillyl moiety and fatty acid chain). As a class, these ‘novel’ compounds are called capsinoids.¹⁰ The acyl residues of capsinoids are identical to those of capsaicinoids.

It has been reported that capsaicin elevates body temperature and suppresses accumulation of fat.^{6,7} However, its use to suppress accumulation of fat is limited due to its strong pungent taste. On the other hand, capsinoids are components of CH-19 Sweet, a non-pungent cultivar of *Capsicum annuum* L., which has weak pungency.^{9,10} Capsiate enhances energy metabolism and suppresses body fat accumulation in mice like capsaicin.¹⁵ A clinical study confirmed that CH-19 Sweet elevates body temperature and increases oxygen consumption in humans.¹⁶ The weaker pungency of capsinoids, as compared with capsaicin, makes it possible

to take advantage of capsinoids' pharmacology (ie, increased energy metabolism and suppression of body fat accumulation) by increasing the amount of capsinoids consumed.

A series of non-clinical studies and a single clinical study have investigated the safety considerations of CH-19 Sweet extract; in those studies, minimal to no toxicity was observed. In a single dose gavage study in rats, transient salivation and decreased motor activity, but no lethality, was observed at the highest dose tested; the reported LD₅₀ being >20 mL CH-19 Sweet extract/kg (equivalent to >1,425 mg capsinoids/kg, or >285 mg DHC/kg) (Watanabe et al 2008a).¹⁸ In that same study, CH-19 Sweet extract was reportedly negative when tested for mutagenicity in *in vitro* and *in vivo* clastogenicity studies. CH-19 Sweet extract, administered daily by gavage in amounts up to 5.0 mL/kg/day (equivalent to 178 mg capsinoids/kg/day or 33 mg DHC/kg/day) failed to induce observable adverse effects (Kodama et al 2008a).¹² Additional published, pre-clinical studies (two generation reproduction in rats [Kodama et al 2008b]¹³ and teratology in rats and rabbits [Bernard et al 2008b]³) failed to detect adverse effects. In the only human study in which CH-19 Sweet extract was administered, 16 healthy male volunteers exhibited no clinically-significant changes in physical examinations, blood pressure, heart rate, body temperature, electrocardiogram, hematology, blood chemistry and urinalysis following consumption of up to 30 mg/person (Bernard et al 2008a).¹

Safety studies of the major component of CH-19 Sweet extract, DHC, also reveal minimal to no toxicity. When a single gavage dose of commercial grade DHC (up to 5,000 mg/kg) was administered to mice, transient clinical alterations, but no lethality (LD₅₀ >5,000 mg/k), were observed over a 14-day period (Watanabe et al 2008b).¹⁹ Testing with both *in vitro* and *in vivo* gene mutation assays suggested a low or extremely low likelihood of inducing genotoxicity (Bernard et al 2008c).⁴ A similar conclusion was reached when DHC was tested in the *in vivo* micronucleus test (Watanabe et al 2008b).¹⁹ Teratology studies performed in rats and rabbits

(high dose 1,000 mg DHC/kg/day) were negative for adverse findings (Bernard et al 2008d).⁵ DHC was administered by gavage (top dose 1,000 mg/kg/day) to rats in two 13-week studies; neither study contained a recovery period. Kodama et al (2008c)¹⁴ concluded the no-observable-adverse-effect-level (NOAEL) was 1,000 mg/kg/day in both sexes. In the absence of a chronic toxicity study and/or evidence of amelioration during a recovery period, Watanabe et al (2008c)²⁰ concluded the NOAEL for males was 300 mg/kg/day and for females was 1,000 mg/kg/day based upon reported minor changes in liver weights, ALT and liver histology. With the generation of chronic and recovery data in a 26-week study, the NOAEL for males was raised to 1,000 mg/kg/day, the same as for females (Kodama et al 2009).¹¹

In comparison to the extensive safety data available on capsinoids and DHC in particular, currently there is no published information on the pharmacokinetics of these substances. As part of the development of capsinoids as a food ingredient, this single (gavage) dose pharmacokinetic study of CH-19 Sweet extract was performed. The study was conducted in compliance with the Law Concerning the Protection and Control of Animals, Law No. 105, October 1, 1973, revised on December 22, 1999, partly revised Law No. 68 on June 22, 2005; Standards Relating to the Care and Management, etc. of Experimental Animals, Notification No. 6, March 27, 1980 of the Prime Minister's Office, Japan, revised on May 28, 2002.

MATERIALS AND METHODS

Animals

Male rats [Crj:CD(IGS) SPF] were purchased from Charles River Japan, Inc. (Kanagawa, Japan). At the time of test article administration, the rats weighed between 204 g and 223 g and were 7 weeks of age. The animals were housed in a SPF animal room under controlled conditions (temperature: 23±3°C; humidity: 50±20%; lighting: 12 h-light/dark cycle [7:00 am to 7:00 pm]). The animals were given *ad libitum* access to a commercially-available diet for rodents (CRF-1, Oriental Yeast Co., Ltd., Tokyo, Japan) and tap water.

The Test Substance and Reagents

CH-19 Sweet extract was prepared by extraction of CH-19 Sweet pepper with *n*-hexane. The content of capsinoids (capsiate, DHC and nordihydrocapsiate) in CH-19 Sweet extract was adjusted to about 7.5% using medium chain triglycerides (Actor M2, Riken Vitamin Co., Ltd., Tokyo, Japan).

Compounds employed as internal reference standards, capsiate, DHC, nordihydrocapsiate and vanillyl undecanoate, were synthesized at Ajinomoto Co., Inc. Vanillyl alcohol (VOH) was purchased from Wako Pure Chemical Industries Ltd., Osaka, Japan, and both β-glucuronidase/arylsulfatase (derived from *Helix pomatia*) and *D*-saccharic acid 1, 4-lactone were purchased from Sigma-Aldrich, St. Louis, USA. All the solvents and other chemicals employed were of HPLC grade or the highest purity commercially-available.

Preparation of Dosing Formulation and Administration Method

CH-19 Sweet extract was diluted with medium chain triglycerides resulting in the production of two concentrations of capsinoids, 2 and 20 mg/mL. Rats were dosed at either 10 or

100 mg capsinoids/kg body weight. Rats were fasted for 16 hr before administration and dosed once by gavage using a stomach tube at a volume of 5 mL/kg body weight.

Sample Collection

Serial blood samples were obtained from the portal vein and abdominal aorta under ether anesthesia at 5, 15 and 30 min, 1, 2 and 4 hr after administration (n=3 at each time point). Blood was drawn into tubes containing 20 mg/mL dichlorvos solution in 0.5 mmol/L sodium citrate buffer at pH 4.3 (Wako Pure Chemical Ind. Osaka, Japan) in a 1 to 10 ratio (dichlorvos-citrate buffer/blood). Plasma was prepared by centrifugation of the blood at 15,000 rpm for 5 min (HITACHI Koki Co., Ltd.). The sampling volume of blood was approximately 500 μ L and 1000 μ L from the portal vein and abdominal aorta, respectively.

Enzymatic Hydrolysis of Metabolites

The plasma, obtained from the abdominal aorta of 3 rats after single oral administration, was pooled and enzymatically hydrolyzed to investigate the conjugates. One mL of the plasma was mixed with 1 mL of 0.5 mol/L acetate buffer, pH 5.0 (Wako Pure Chemical Ind. Osaka, Japan) and 50 μ L of β -glucuronidase (approximately 100,000 Fishman units/mL) and arylsulfatase (approximately 800,000 Roy units/mL). In the inhibition experiment, 20 mg of *D*-saccharic acid 1, 4-lactone, a β -glucuronidase inhibitor was added to the mixture and the mixture was incubated at 37°C for 4 hr to hydrolyze the conjugates. After incubation, the samples were treated as described later in this paper.

Pretreatment for the Measurement of Capsinoids

An OASIS hydrophilic-lipophilic balance cartridge (60 mg/3 mL, Waters Corporation, Milford, MA, USA) was selected for the solid phase extraction. The cartridge was activated using

ethyl acetate (Junsei Chemical Co., Ltd. Tokyo, Japan) and brought to equilibration with methanol (Junsei Chemical Co., Ltd. Tokyo, Japan) and water prior to use. One hundred μL of plasma were mixed with 10 μL of internal standard solution and 200 μL of acetonitrile (Junsei Chemical Co., Ltd. Tokyo, Japan). After centrifugation, the upper layers were mixed with 950 μL of 20 mmol/L phosphate buffer at pH 3.0 (Wako Pure Chemical Ind. Osaka, Japan) and the mixture was applied to the solid phase extraction cartridge. The cartridge was washed with 1 mL of 0.1% TFA solution (Wako Pure Chemical Ind. Osaka, Japan) and 30% acetonitrile aqueous solution. The analytes were eluted with 1 mL of ethyl acetate into a disposable glass tube containing 2 μL of DMSO (Junsei Chemical Co., Ltd. Tokyo, Japan). The solvents were evaporated to dryness under a gentle stream of nitrogen at ambient temperature. The dried residue was reconstituted in a mixture of 20 mmol/L phosphate buffer (pH 3.0)/acetonitrile (50/50; v/v).

All the procedures executed prior to the application of the sample to the solid phase extraction column were performed on ice and completed within 1 hr.

Pretreatment for the Measurement of VOH

An OASIS hydrophilic-lipophilic balance cartridge (30 mg/1 cc, Waters Corporation, Milford, MA, USA) was selected for the solid phase extraction. The cartridge was activated using acetonitrile and brought to equilibration with water prior to use. One hundred μL of plasma were mixed with 200 to 500 μL of 50 mmol/L phosphate buffer (pH 3.0) under ice-cold conditions and the mixture was applied to the solid phase extraction cartridge. The cartridge was washed with 1 mL of 0.1% TFA solution and 1 mL of 10% methanol solution. The analytes were eluted with 1 mL of acetonitrile into a disposable glass tube containing 2 μL of DMSO. The solvents were evaporated to dryness under a gentle steam of nitrogen at ambient temperature. The dried residue was reconstituted in 200 μL of water and injected into the HPLC.

LC-MS/MS Analysis for Capsinoids

HPLC separation was performed using Agilent 1100 (Agilent Technologies, Santa Clara, U.S.A.) or Shimadzu 10A (Shimadzu Corporation, Kyoto, Japan) system equipped with an Inertsil Ph-3 (4.6 mm i.d. × 150 mm 3 μm GL-Science Inc., Tokyo, Japan) analytical column and SUMIPAK Filter PG-ODS (4×4 mm i.d., Sumika Chemical Analysis Service Ltd., Tokyo, Japan) guard filter. The mobile phase was a mixture of water/methanol (35:65; v/v) and the flow rate was maintained at 0.8 mL/min. The analytical cycle was maintained at ≤20 min. The HPLC system was connected to an API2000 MS/MS system (Applied Biosystems, Foster City, CA U.S.A), operated in APCI positive mode. The interface temperature was 450°C and nitrogen was used as nebulizer and collision gas (collision energy: 31 eV); the corona discharge current was set to 2 μA. The MS/MS system was focused in multiple reaction monitoring (MRM) mode to monitor the ion as Q1: 137.1 and Q3: 94.2. Data collection and analysis were performed with Analyst (AB/MDS, SCIEX).

HPLC Analysis for VOH

The analysis of VOH in plasma was performed using a Shimadzu LC system which included a DGU-14A degasser, LC-10ADVP pump, SIL-HTC auto-sampler, CTO-10AVP oven column, and SPD-10A UV detector (Shimadzu Corporation, Kyoto, Japan). A guard column (Inertsil Diol [3.0 mm i.d. x 10 mm, 5 μm] GL-Science Inc., Tokyo, Japan), precolumn (Inertsil Diol [3.0 mm i.d. x 150 mm, 5 μm] GL-Science Inc.) and analytical column (Cadenza CL-C18 [3.0 mm i.d. x 150 mm, 3 μm] Imtakt Corporation, Kyoto, Japan) were employed. These columns were assembled into a column-switching system. The mobile phase was a mixture of 20 mmol/L phosphate buffer (pH 7.0)/methanol (90/10, v/v) and the flow rate was 0.4 mL/min. The analytical cycle was maintained at ≤18 min. The eluted solution was monitored by absorbance at

280 nm. Data collection and analysis were performed using Class VP (ver 6.12 SP3, Shimadzu Corporation, Kyoto, Japan).

Calculation of VOH Conjugate Concentrations

In order to investigate the concentration of sulfate and glucuronide VOH conjugates in plasma, the following analyses were performed:

1. The concentration of plasma VOH was determined following incubation with 0.5 mol/L acetate buffer, pH 5.0;
2. The concentration of plasma VOH was determined following incubation with 0.5 mol/L acetate buffer, pH 5.0 and β -glucuronidase;
3. The concentration of plasma VOH was determined following incubation with 0.5 mol/L acetate buffer, pH 5.0, β -glucuronidase, and *D*-saccharic acid 1, 4-lactone, and β -glucuronidase.

The concentration of the VOH sulfate conjugate was defined as the difference between 3. and 1. above, while the concentration of the VOH glucuronide conjugate was defined as the difference between 2. and 3.

Calculation of Pharmacokinetic (PK) Parameters

The maximum plasma concentration (C_{\max}) and the time to attain C_{\max} (T_{\max}) were calculated from the mean plasma concentrations at each time point. The area under the plasma concentration versus time curve (AUC_{0-lim}) was calculated from the mean plasma concentrations at each time point by the trapezoidal method using Microsoft Excel. The plasma elimination half-life ($t_{1/2}$) was calculated as follows. The time points which reflected an elimination phase were obtained from the plasma concentration versus time curve. The mean plasma concentration

values at each time point were converted to logarithmic values. Subsequently, a linear curve of the elimination phase was calculated based on the above (curve and log values) and using the method of least squares. Finally, a $t_{1/2}$ was calculated from the slope of the curve.

RESULTS

The levels of the capsinoids in the portal vein and systemic blood of all rats (both 10 and 100 mg/kg) were below the limit of quantitation (LOQ – capsiate, DHC and nordihydrocapsiate, 50 ng/mL) at all time points examined. Thus, no pharmacokinetic parameters could be calculated for these compounds.

The plasma concentrations of free VOH determined in the portal vein and systemic blood of rats are presented in Table 1. The LOQ for VOH was 20 ng/mL. The free VOH pharmacokinetic parameters derived from the Table 1 data are presented in Table 2. The time to the maximum concentration (T_{max}) of VOH in the portal vein was 30 min after administration in both 10 and 100 mg/kg dose groups, while the maximum concentrations (C_{max}) achieved at T_{max} were 0.163 µg/mL and 1.48 µg/mL, respectively. AUC_{0-4hr} in the 10 and 100 mg/kg dose groups were 0.321 µg·hr/mL and 3.85 µg·hr/mL, respectively.

As there were no appropriate time points reflecting an elimination phase based on the results of plasma concentration-time profile, calculation of $t_{1/2}$ was not possible.

In rats dosed with 10 mg/kg, the systemic plasma concentrations of VOH were below the limit of quantitation at all time points. In rats dosed with 100 mg/kg, the systemic plasma concentration of VOH was 0.0246 ± 0.0241 µg/mL at 5 min after administration, but fell below the LOQ at each time point thereafter. The AUC_{0-5min} for the 100 mg/kg group was 0.00103 µg·hr/mL; the $t_{1/2}$ could not be determined.

Figure 3 and Table 3 show the time course of VOH conjugate concentrations. In the 10 mg/kg dose group, the concentrations of the sulfate conjugate were generally higher than the concentrations of the glucuronide. The AUC_{0-4hr} of the VOH sulfate conjugate was 2.27 $\mu\text{g}\cdot\text{hr}/\text{mL}$, while that of the glucuronide was 1.80 $\mu\text{g}\cdot\text{hr}/\text{mL}$.

In the 100 mg/kg dose group, the concentrations of sulfate conjugate of VOH were higher than the concentrations of the glucuronide at all the time points. The AUC_{0-4hr} of the vanillyl alcohol sulfate conjugate was 18.2 $\mu\text{g}\cdot\text{hr}/\text{mL}$ and that of glucuronide was 8.94 $\mu\text{g}\cdot\text{hr}/\text{mL}$.

DISCUSSION

The results of this pharmacokinetic and metabolism study were obtained following a single gavage dose of CH-19 Sweet extract containing 7.5% capsinoids (equivalent to 10 or 100 mg capsinoids/kg) to fasting male rats. No measureable levels of any of the capsinoids (ie, capsiate, DHC and nordihydrocapsiate) were obtained in either the portal vein or systemic plasma at any study time points using a LOQ of 50 ng/mL . These findings are consistent with a previous study which reported that following a single gavage administration of ^{14}C -dihydrocapsiate to male rats, DHC was not detected in circulating plasma.² Similarly, a study in human volunteers reported that following an ingestion of up to 30 mg/kg capsinoid, neither capsinoids nor VOH were detectable in the plasma.¹ These results suggest that almost all, if not all, of the administered capsinoids were metabolized either in the gastrointestinal tract or alimentary mucosa or both prior to absorption into the portal vein. However, these data cannot exclude the possibility of extremely rapid metabolism in the portal vein.

The data further document that VOH, a metabolite of capsinoids, was found in the portal vein and had pharmacokinetic parameters (C_{max} and AUC_{0-4hr}) which were directly proportional to dosage. The apparent T_{max} of VOH in the portal compartment (30 minutes) is in agreement

with that reported (40 minutes) in a previous study (Bernard et al 2009).² VOH was, in turn, broken down (either prior to or immediately after its release into the systemic plasma) to sulfuric and glucuronic acid conjugates. Levels of both conjugates in the plasma were directly proportional to dose; that is, the plasma levels of both conjugates increased with increasing dose (ie, 10 vs. 100 mg/kg). However, the plasma levels of the sulfuric conjugates were consistently higher than those of glucuronide in both dosage groups. This suggests that, at least in rats, sulfuration plays a bigger role in the metabolism of VOH than does glucuronidation in rats. The proposed metabolic pathway for orally-administered capsinoids is presented in Figure 4.

Previously published toxicity and safety studies reported a lack of severe adverse effects following the administration of either CH-19 Sweet extract^{1,3,12,13,17,18} or DHC.^{2,4,5,11,14,19,20} In one of these studies,¹¹ rats were administered 100, 300 and 1,000 mg DHC/kg/day for 26 weeks with resulting NOAELs of 1,000 mg/kg/day for both sexes. This result suggests that VOH and VOH metabolites, sulfuric and glucuronic acid conjugates, the metabolites of the capsinoids contained in CH-19 Sweet extract, when administered to rats, caused no severe adverse events at those doses as would be expected based upon a structure-activity analysis.

A major component of capsinoids is DHC. In a previously performed study,² the metabolite profiles for DHC, both before and after enzymatic hydrolysis, were evaluated and the results suggest that the compound is most likely to be metabolized in a multi-step process. DHC is initially hydrolyzed to yield VOH and 8-methyloctanoic acid. Subsequently, the majority of the VOH is predominantly conjugated with glucuronic or sulfuric acid, while minor amounts are oxidized to vanillic acid.

In the only human clinical study reported for CH-19 Sweet extract,¹ the authors concluded that the consumption of either 15 or 30 mg capsinoids/person was without clinically-significant changes, and neither capsinoids nor VOH were detectable in the plasma. The pharmacokinetic

results of the current rat study are consistent with and expand upon the findings previously reported in humans.

CONCLUSIONS

Based upon the results of this study, a metabolic pathway for the capsinoids (capsiate, DHC and nordihydrocapsiate) is suggested. The results are consistent with the rapid and apparently complete metabolism of capsinoids in the GI tract and/or alimentary canal to VOH, although extremely rapid metabolism in the portal vein cannot be excluded by these data. VOH subsequently undergoes rapid and apparently complete metabolism as demonstrated by the detection of sulfuric and glucuronic acid conjugates not VOH in the systemic plasma. These results are consistent with what is known regarding the human pharmacokinetics of capsinoids and support the pre-clinical toxicology and safety studies which suggest that capsinoids have a low potential for toxicity.

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TABLE 1.

Plasma concentration of vanillyl alcohol following
a single oral administration of capsinoids to rats.

Time (hr)	Plasma concentration of vanillyl alcohol ($\mu\text{g/mL}$)*			
	Portal vein plasma		Systemic plasma	
	10 mg/kg	100 mg/kg	10 mg/kg	100 mg/kg
0.083	0.0484 \pm 0.059	1.44 \pm 0.36	N.D.	0.0246 \pm 0.0241
0.25	0.101 \pm 0.032	1.08 \pm 0.28	N.D.	N.D.
0.5	0.163 \pm 0.022	1.48 \pm 0.27	N.D.	N.D.
1	0.111 \pm 0.017	0.858 \pm 0.809	N.D.	N.D.
2	0.0555 \pm 0.0378	0.818 \pm 0.447	N.D.	N.D.
4	0.0657 \pm 0.0234	1.02 \pm 0.50	N.D.	N.D.

*Each value represents Mean \pm S.D. of 3 individuals.

Where the concentration of 2 or 3 of 3 cases was <LOQ (20 $\eta\text{g/mL}$), the result is expressed as N.D.

Where the concentration of 1 of 3 cases was <LOQ, the result is expressed as Mean \pm S.D. on the assumption that such value is zero (0).

TABLE 2.

Pharmacokinetic parameters of vanillyl alcohol
following a single oral administration of capsinoids to rats.

	Vanillyl alcohol			
	Portal vein plasma		Systemic plasma	
	10 mg/kg	100 mg/kg	10 mg/kg	100 mg/kg
AUC _{0-4hr} ($\mu\text{g} \cdot \text{hr/mL}$)	0.321	3.85	N.C.	0.00103
C _{max} ($\mu\text{g/mL}$)	0.163	1.48	N.C.	0.0246
T _{max} (hr)	0.500	0.500	N.C.	0.0833
t _{1/2} (hr)	N.C.	N.C.	N.C.	N.C.

Parameters that cannot be calculated (LOQ <20 $\eta\text{g/mL}$) are expressed as N.C.

Values were calculated from pooled plasma (N=3) at each time point.

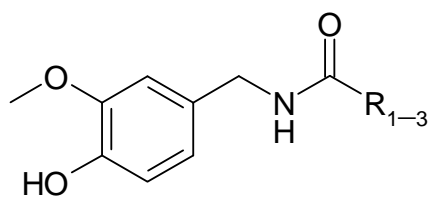
TABLE 3.

Vanillyl alcohol conjugates: Plasma concentrations following dose administration.

Time (hr)	Concentrations of sulfate of vanillyl alcohol (µg/mL)		Concentrations of glucuronide of vanillyl alcohol (µg/mL)	
	10 mg/kg	100 mg/kg	10 mg/kg	100 mg/kg
0.083	0.124	2.01	0.146	0.864
0.25	0.602	5.91	0.444	2.70
0.5	0.829	5.04	0.562	1.32
1	1.05	5.96	0.545	3.24
2	0.501	3.86	0.372	1.63
4	0.275	4.58	0.515	2.90

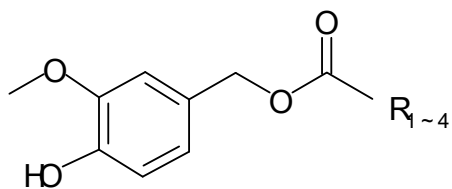
The figure represents time course of concentrations of conjugates of vanillyl alcohol in systemic plasma after single oral administration of capsinoids in rats at doses of 10 mg/kg and 100 mg/kg

Figure 1. Chemical structure of capsaicinoids



Capsaicin	R ₁	
Dihydrocapsaicin	R ₂	
Nordihydrocapsaicin	R ₃	

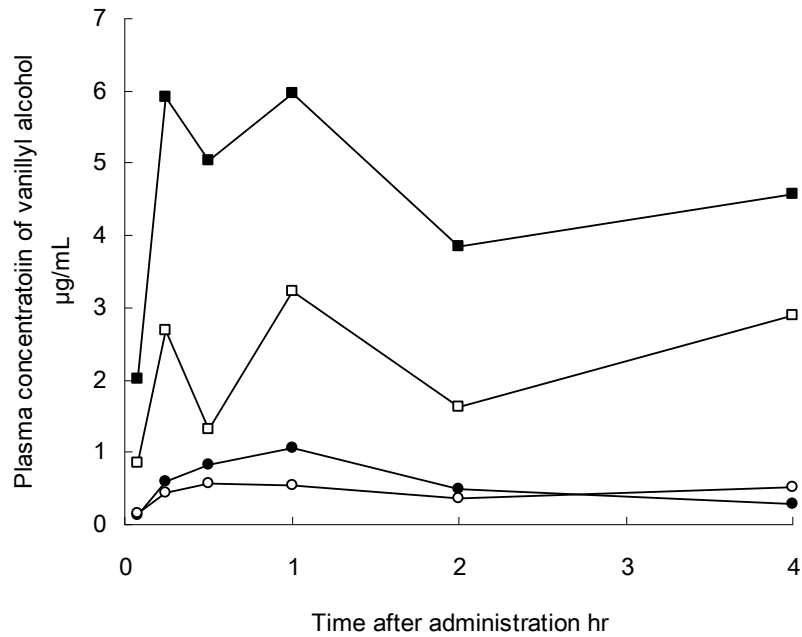
Figure 2. Chemical structure of capsinoids



Capsiate (CST)	R ₁	
Dihydrocapsiate (DCT)	R ₂	
Nordihydrocapsiate (NDCT)	R ₃	
Vanillyl undecanoate (IS)	R ₄	

FIGURE 3

Time course of vanillyl alcohol conjugates concentrations. The figure represents time course of concentrations of conjugates of vanillyl alcohol in systemic plasma after single oral administration of capsinoids in rats at doses of 10 mg/kg and 100 mg/kg.



- : Concentration as glucuronide at 100 mg/kg
- : Concentration as sulfate at 10 mg/kg.
- : Concentration as glucuronide at 10 mg/kg.
- : Concentration as sulfate at 100 mg/kg.
- : Concentration as glucuronide at 100 mg/kg

Figure 4. Metabolic pathway of capsinoids and vanillyl alcohol

