# Pharmacokinetic and The Effect of Capsaicin in *Capsicum frutescens* on Decreasing Plasma Glucose Level

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***Background:*** *The active substance found in Capsicum frutescens (capsicum) that gives hot and spicy flavor is capsaicin, and it seems to have many pharmacological effects.*
***Objective:*** *The present research was conducted to study the effect of capsicum on plasma glucose level and to correlate its action with the pharmacokinetic properties of capsaicin in capsicum.*
***Material and Method:*** *The crossover study was performed in 12 healthy volunteers by performing the OGTT while receiving placebo or 5 grams of capsicum. The insulin secretion and capsaicin level in plasma were measured using the HPLC method.*
***Results:*** *The results of the OGTT showed that plasma glucose levels in volunteers who received capsicum were significantly lower than those in the placebo group at 30 and 45 minutes ($p < 0.05$). Furthermore, plasma insulin levels were significantly higher at 60, 75, 105, and 120 minutes ($p < 0.05$). When comparing before and after capsicum intake, the results showed the insulin levels were maintained. The pharmacokinetic parameters of capsaicin shown as $C_{max}$, $T_{max}$, $AUC_{0-t}$, $T_{1/2}$ are 2.47 $\pm$ 0.13 ng/ml, 47.08 $\pm$ 1.99 min, 103.6 $\pm$ 11.3 ng.min/ml, and 24.87 $\pm$ 4.97 min, respectively.*
***Conclusion:*** *In conclusion, the present study found that 5 grams of capsicum presented capsaicin levels that were associated with a decrease in plasma glucose levels and the maintenance of insulin levels. The present result might have clinical implications in the management of type 2 diabetes.*

***Keywords:*** *Capsaicin, Capsicum frutescens, Pharmacokinetic, Insulin, Plasma glucose*

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*Capsicum frutescens* is a household vegetable that has been consumed for a long time. The active substance that gives the hot and spicy flavor was identified as capsaicin[1]. A number of research studies have shown multiple pharmacological effects of capsaicin on a variety of physiological systems such as cardiovascular system, gastro-intestinal tract, metabolic rate, and pain relief[1,2].

The action of capsaicin is mediated by TPRV1 (vanilloid receptor), which belongs to an ion channel group. Not only capsaicin but also heat, proton, and Resiniferatoxin (RTX) can activate this receptor leading to many physiological effects[3-5]. Akiba Y et al first reported the discovery of TPRV1 on the beta cells of pancreas and found that capsaicin could activate this receptor resulting in an increase in insulin secretion[6]. Chaiyata P et al found that capsicum could decrease the plasma glucose levels but the actual mechanism was unknown[1], while Monsereenusorn et al reported that capsaicin could inhibit the glucose absorption into bloodstream[7-9]. On the contrary, Gyula et al reported that pure capsaicin activated glucagon secretion and increased the plasma glucose level[10]. Therefore, the effect of capsaicin on plasma glucose levels in humans is still conflicting.

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There are some researches about the pharmacokinetic of capsaicin on plasma glucose level in testing animals but the results are inconsistent. The aim of the present research was to study the effect of capsicum, which provides capsaicin as an active compound, on plasma glucose and insulin levels in healthy volunteers and to study the pharmacokinetic properties of capsaicin.

## Material and Method

### *Subject*

The present study was approved by the Ethic Committee of the Faculty of Medicine, Chulalongkorn University. Twelve healthy male volunteers were recruited in the present study. All were considered healthy by physical examination, and had no history of capsicum allergy, gastrointestinal, liver, and renal diseases. They can tolerate hot spicy food well. They were nonsmokers. All of them abstained from alcohol and medications at least one month before the present study[11,12]. Furthermore, they had to abstain from capsaicin-containing food for at least seven days before the present study. The method and condition of the present study were clearly explained to all participants. Informed consent was signed and obtained from each person prior to entering the experiment.

**Table 1.** Demographic and clinical laboratory data of subjects recruited in the study (n = 12)

| Demographic and clinical laboratory data | Mean ± SD |
|---|---|
| Sex | Male |
| Age (year) | 21.83 ± 1.47 |
| BW (kg) | 65.80 ± 6.51 |
| Ht (m) | 1.74 ± 0.05 |
| BMI | 21.80 ± 1.40 |
| PR | 70.92 ± 7.65 |
| SBP (mmHg) | 108.33 ± 10.30 |
| DBP (mmHg) | 75.00 ± 7.07 |
| Hemoglobin (g/dl) | 14.62 ± 0.91 |
| Hematocrit (%) | 43.81 ± 2.45 |
| Glucose (mg/dl) | 86.50 ± 5.00 |
| BUN (mg/dl) | 11.83 ± 2.75 |
| Creatinine (mg/dl) | 0.89 ± 0.13 |
| AST (U/L) | 19.50 ± 4.98 |
| ALT (U/L) | 17.58 ± 7.89 |
| Alkaline phosphatase (U/L) | 59.17 ± 15.28 |
| Anti HIV | Negative |
| HBsAg | Negative |

### *Chemical and instrument*

The fresh capsicum that was used throughout the present study came from the same lot and appeared in a green color, weighed approximately 0.6 gram per piece and was obtained from Pathum Thani, Thailand. Five grams of capsicum provided 26.6 milligram of capsaicin as tested by the Department of Pharmaceutical Technology, Faculty of Pharmaceutical Science, Naresuan University.

Capsaicin standard was obtained from Sigma Chemical Co, Germany. Acetonitrile, diethyl ether, acetic acid, and methanol (HPLC grade) were obtained from MERCK, Germany.

High-performance liquid chromatography (HPLC): Spectra system isocratic pump (PC1000), Spectra system autosamples (AS3000), Spectra system fluorescence detector, Spectra system SN 4000, and Computer and a software program P1000 were from Thermo separation product. Column was use μ-bondapak size 250 x 4.6 millimeters with silica C18 size 5 microns were obtained from Water Associates, USA.

### *Study design*

After an 8-hour overnight fast, the subjects were given 75 grams of glucose diluted in 150 ml of water for oral glucose tolerance test (OGTT). Then they were administered capsicum (5 g) contained in a gelatin capsule or placebo. Blood samples were collected every 15 minutes until 2 hours to measure the glucose level. The crossover was done after a one-week washout period.

For insulin baseline determination, after an overnight fast, all subjects were given a placebo and the serum samples were collected every 15 minutes for 2 hours. After that they were given 5 grams of capsicum, the blood samples were collected to measure the insulin level using the same process. To measure capsaicin level, blood samples were collected every 10 minutes for the first 1 hour and every 15 minutes for the next hour.

The research was carried out according to Good Clinical Practice (ICH/GCP) guidelines. The research protocol was approved by the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand.

### *Methods*

Plasma glucose level was measured by a standard glucose oxidase assay[13]. Serum Insulin level was measured by an electrochemiluminescent

immunoassay using Elecsys 2010/1010 machine[14]. Plasma capsaicin level was measured by an HPLC method using column C18 and mobile phase, which was composed of water, acetonitrile and acetic acid in the ratio of 50:50:1. A fluorescence detector was used for capsaicin measurement.

Method for capsaicin analysis was validated following Guidance for industry: Bioanalytical method validation (U.S. Department of Health and Human Series FDA, CDER, CVM. May 2001, BP).

### *Statistical analysis*

The data including plasma glucose level, serum insulin level and plasma capsaicin level were demonstrated as mean ± S.E.M. ANOVA for two-way crossover design was used to analyze the difference in plasma glucose level at each time point between the capsicum group and the placebo group. One-way ANOVA was used to analyze the changes in serum insulin level at different time points compared to that before the test. Pair t-test was used to analyze the difference in insulin level at each time point and the area under the curve (AUC) of serum insulin and plasma glucose levels between the two groups. The result was considered significant if a p-value was less than 0.05.

## Results

Plasma glucose levels were lower in volunteers given capsicum than those in the placebo group, which were statistically significant at 30 and 45 min ($p < 0.05$) (Fig. 1). The AUC of plasma glucose level vs. time in the capsicum group was also significantly less than that in the placebo group (12,686.6 ± 457.9 mg.min/dl vs. 14,265.5 ± 631.5 mg.min/dl, $p < 0.05$). The insulin levels in the capsicum group were significantly higher than those in the placebo group at 60, 75, 105, and 120 min ($p < 0.05$), as shown in Fig. 2. Additionally, the AUC of insulin level vs. time of in the capsicum group was significantly higher than that in the placebo group (526.4 ± 86.9 microIU.min/dl vs. 332.3 ± 69.7 microIU.min/dl, $p < 0.05$).

In the comparison of insulin level before and after the intervention, it was found that when the placebo was given, the insulin levels were significantly decreased continuously at 60, 75, 105, and 120 min ($p < 0.05$). In contrast, when capsicum was given, there were no different changes in the insulin level compared to that before received capsicum. This result suggested that the insulin levels were maintained when capsicum was taken.

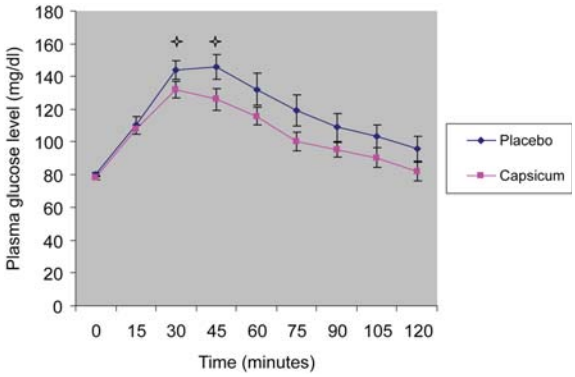


**Fig. 1** Change in plasma glucose levels after an OGTT (n = 12). Comparison between capsicum and placebo group. The results are expressed as mean ± S.E.M. (✧ statistical significant different, $p < 0.05$)

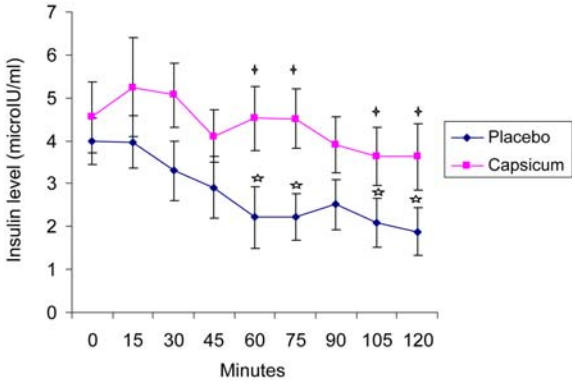


**Fig. 2** Changes in serum levels of insulin (n = 12). Comparison between capsicum and placebo group. The results are expressed as mean ± S.E.M. (+ significant different, $p < 0.05$ between group, ☆ significant different $p < 0.05$ compared with time 0)

### *Pharmacokinetic study of capsaicin in Capsicum frutescens*

After capsicum ingestion, capsaicin can be first detected in the plasma at 10 minutes. The peak plasma concentration ($C_{max}$) of capsaicin was 2.47 ± 0.13 ng/ml and $T_{max}$ 47.08 ± 1.99 minutes. The amount of capsaicin absorbed into the body as presented by $AUC_{0-t}$ was 103.6 ± 11.3 ng.min/ml. The results are shown in Table 2. The mean pharmacokinetic profile of plasma capsaicin level vs. time of all 12 healthy volunteers is illustrated in Fig. 3.

**Tabel 2.** Pharmacokinetic parameters of capsaicin in healthy volunteers (n = 12)

| Pharmacokinetic parameters | Mean ± S.E.M. |
|---|---|
| $C_{max}$ (ng/ml) | 2.47 ± 0.13 |
| $T_{max}$ (minute) | 47.08 ± 1.99 |
| $AUC_{0-t}$ (ng.min/ml) | 103.60 ± 11.3 |
| $T_{1/2}$ (minute) | 24.87 ± 4.97 |

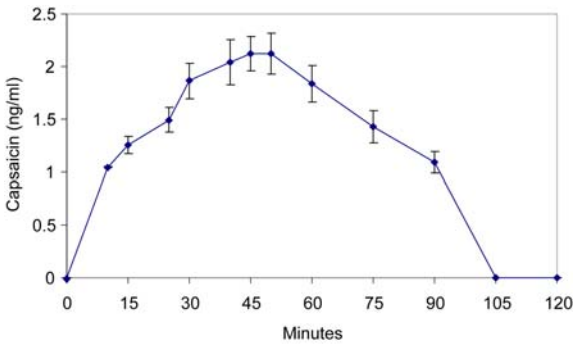


**Fig. 3** Pharmacokinetic profile of capsaicin in healthy volunteers (n = 12), (mean ± S.E.M.)

## Discussion

The present study showed that intake of 5 grams of fresh capsicum, which contained approximately 26.6 milligrams of capsaicin by OGTT test, was associated with lower plasma glucose levels at 30 and 45 minutes. In addition, those who took fresh capsicum had significantly higher insulin levels and insulin amount compared to those in the placebo group. Furthermore, it has been found that the insulin levels were maintained to the basal level after intake capsicum compared with continuously decreased insulin level in the placebo group.

The results of the present study are consistent with a previous report by Tolan et al. They performed the test on canines under OGTT method and found that the fresh capsicum had lower plasma glucose levels and higher insulin levels than those in the placebo group. They suggested that plasma glucose decrease could be caused by capsicum inducing insulin-secretion[15,16]. Akiba et al has reported that the capsaicin receptor (TRPV1) is expressed on the beta cells of the pancreas and capsaicin could induce insulin secretion from the pancreas. It has been suggested that the effect of capsaicin on insulin secretion is due to more calcium influx into the cells[6]. Beside the effect on insulin secretion, capsaicin may decrease plasma glucose by other mechanisms since Monsereenusorn et al found that capsaicin could inhibit glucose absorption from the intestine in canines and rodents[8,9].

The present study also proved the question of whether capsaicin from capsicum can be absorbed into the body and that can support the decreasing plasma glucose of capsicum might be from this active substance. Up to now, there has been no report of the pharmacokinetic study of capsaicin in human. The only study was performed in in situ of white guinea pigs, which showed that the absorption of capsaicin occurred in many parts of the gastrointestinal tract. Capsaicin was absorbed 50% in the stomach, 80% in the jejunum part, and 70% in the ileum part. The result showed that capsaicin was best absorbed in the jejunum and was a non-energy consumed absorption, which was absorbed into a portal system excluding mesenteric lymphangial. In the present study, the authors developed a method for capsaicin detection in the circulation, which showed good accuracy and precision. The lower limit of quantization of capsaicin was 0.93 ng/ml. This research found that capsaicin was absorbed so rapidly that it could be detected at 10 minutes after ingestion. Furthermore, capsaicin was rapidly metabolized as the half-life of capsaicin was 24.87 ± 4.97 minutes and the capsaicin level was maintained only to 90 minutes. These results are consistent with a short $T_{1/2}$ value of capsaicin in rats reported by Surh et al[2]. The rate and extent of capsaicin absorption into the body in the terms of $C_{max}$, $T_{max}$ and $AUC_{0-t}$ were 2.47 ± 0.13 ng/ml, 47.08 ± 1.99 minutes and 103.6 ± 11.3 ng.min./ml, respectively. The low $C_{max}$ of capsaicin could also be explained by the rapid metabolism while being absorbed. Kawada et al and Leelahuta et al have previously demonstrated that in white guinea pigs, capsaicin was metabolized by CYP2E1 into N-(4,5-dihydroxyl-3-methoxybenzyl)-acylamide, which is a catechol, and other substances such as vanillic acid[17].

The time course of capsaicin level in the plasma after ingestion was correlated to the time of plasma glucose decreasing and serum insulin maintaining. The authors found that capsaicin was detectable in the bloodstream starting at 15 minutes until 90 minutes, which was followed by a decrease in plasma glucose levels from 15 minutes until 120 minutes and the maintenance in insulin level from the basal level until 120

minutes. The significant difference in plasma glucose levels at 45 minutes was also correlated to $C_{max}$ of capsaicin at 45 minutes.

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## เภสัชจลนศาสตร์ของสาร capsaicin ในพริกขี้หนูสดและฤทธิ์ทางเภสัชวิทยาของพริกขี้หนูสดต่อน้ำตาลในเลือดในอาสาสมัครสุขภาพดี

กมล ไชยสิทธิ์, วีระพันธุ์ โชควิฑูรกิจ, สุพีชา วิทยเลิศปัญญา

**ภูมิหลัง**: พริกขี้หนูสดเป็นพืชผักสวนครัวที่บริโภคกันมาช้านาน และได้มีการค้นพบสารสำคัญในพริกขี้หนูที่ทำให้เกิดความเผ็ดร้อนคือ capsaicin และพบว่า capsaicin ส่งผลกระทบต่อระบบต่าง ๆ ในร่างกายได้หลายระบบ
**วัตถุประสงค์**: ศึกษาฤทธิ์ของพริกขี้หนูสดต่อการลดระดับน้ำตาลในเลือด และหาค่าเภสัชจลนศาสตร์ของ capsaicin ในพริกขี้หนู
**วัสดุและวิธีการ**: อาสาสมัครสุขภาพดีจำนวน 12 คน ให้อาสาสมัครทำ OGTT ร่วมกับการได้รับ placebo และพริกขี้หนูสดขนาด 5 กรัม จากนั้นให้อาสาสมัครกลุ่มเดิมได้รับ placebo และพริกขี้หนูสดขนาดเดียวกัน เพื่อศึกษาการกระตุ้นการหลั่งอินซูลินและวัดระดับของ capsaicin ในเลือดโดยใช้เครื่อง HPLC
**ผลการศึกษา**: ผลการศึกษาพบว่าอาสาสมัครกลุ่มที่ได้รับพริกขี้หนูสดร่วมกับการทำ OGTT มีระดับน้ำตาลในเลือดต่ำกว่ากลุ่มที่ได้รับ placebo โดยที่เวลา 30 และ 45 นาทีมีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ ($p < 0.05$) และอาสาสมัครกลุ่มที่ได้รับพริกขี้หนูสดมีระดับอินซูลินสูงกว่ากลุ่มที่ได้รับ placebo โดยที่เวลา 1 ชั่วโมง, 1 ชั่วโมง 15 นาที, 1 ชั่วโมง 45 นาที และ 2 ชั่วโมงมีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ ($p < 0.05$) และค่าเภสัชจลนศาสตร์ของ capsaicin ได้แก่ ค่า $C_{max}$ เท่ากับ 2.47 $\pm$ 0.46 นาโนกรัม/มิลลิลิตร ค่า $T_{max}$ เท่ากับ 47.08 $\pm$ 6.89 นาที ค่า $AUC_{0-t}$ เท่ากับ 103.6 $\pm$ 38.99 นาโนกรัม.นาที/ มิลลิลิตร และค่า $T_{1/2}$ เท่ากับ 24.87 $\pm$ 17.2 นาที
**สรุป**: จากการศึกษาพบว่าพริกขี้หนูสดขนาด 5 กรัมมีคุณสมบัติในการลดระดับน้ำตาลในเลือด และสามารถกระตุ้นการหลั่งอินซูลินได้ โดยผลที่ได้น่าจะมาจาก capsaicin เข้าสู่ร่างกายและออกฤทธิ์กระตุ้นการหลั่งอินซูลิน และจากผลการศึกษานี้อาจนำไปสู่การใช้ประโยชน์ในผู้ป่วยเบาหวานชนิดที่ 2 ต่อไป