

Anti-hyperglycemic Effect of Fangchinoline Isolated from *Stephania Tetrandra Radix* in Streptozotocin-Diabetic Mice

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Kampo medicine, *Stephania tetrandra Radix* (*Stephania*) in Boi-ogi-to increases the blood insulin level and falls the blood glucose level in streptozotocin (STZ)-diabetic ddY mice. These actions of *Stephania* are potentiated by *Astragalus membranaceus* Bunge *Radix* (*Astragali*) in Boi-ogi-to (Liu *et al.*, *J. Traditional Med.*, 17, 253–260, 2000). In the present study, actions of bis-benzylisoquinoline alkaloids isolated from *Stephania* were investigated in the hyperglycemia of STZ-diabetic mice. A main bis-benzylisoquinoline alkaloid, fangchinoline (0.3–3 mg/kg) significantly fell the blood glucose level of the diabetic mice in a dose-dependent manner. The effect of fangchinoline was 3.9-fold greater than that of water extract of *Stephania*. However, another main compound, tetrandrine (1–100 mg/kg) did not have any effect. The water extract of *Astragali* did not affect singly but potentiated the anti-hyperglycemic action of fangchinoline (0.3 mg/kg). Out of used compounds (1 mg/kg) isolated from *Stephania*, fangchinoline, fangchinoline 2'-N- α -oxide and 2'-N-norfangchinoline, which are substituted with 7-hydroxy side chain for 7-O-methyl side chain, decreased to near 50% of high blood glucose level. In addition, tetrandrine 2'-N- β -oxide, tetrandrine 2'-N- α -oxide, tetrandrine 2-N- β -oxide, fangchinoline 2'-N- α -oxide, which are added to 2- or 2'-N-oxide side chain, also decreased to near 50% of the high blood glucose level. In conclusion, fangchinoline but not tetrandrine from *Stephania* shows the anti-hyperglycemic action in the STZ-diabetic mice. The demethylation of 7-O-position and/or addition of 2- or 2'-N-oxide side chain in bis-benzylisoquinoline compounds in *Stephania* have a role for the induction of the anti-hyperglycemic actions.

Key words fangchinoline; *Stephania tetrandra Radix*; anti-hyperglycemic action; combined effect; *Astragali Radix*; streptozotocin-diabetic mouse

A Kampo medicine, Boi-ogi-to (Fang-ji-huang-qi-tang), is one of the traditional prescriptions and consists of *Stephania tetrandra Radix* (*Stephania*), *Astragali Radix* (*Astragali*), *Atractylodes Lancea Rhizoma*, *Glycyrrhizae Radix*, *Zingiberis Rhizoma* and *Zizyphi Fructus*. Boi-ogi-to has long been used clinically in the treatment of arthritis and edema in China and Japan. Boi-ogi-to is also suggested to improve indirectly an abnormal metabolism of glucose and lipid in diabetic patients with obesity.¹ We have previously reported that Boi-ogi-to increases blood insulin level and decreases blood glucose level in streptozotocin (STZ)-diabetic mice. The anti-hyperglycemic action of Boi-ogi-to depends on the action of *Stephania* but not *Sinomeni Caulis ET Rhizoma* in the prescription.² *Astragali* does not have a direct anti-hyperglycemic effect but potentiates the actions of *Stephania* on blood levels of glucose and insulin.³

Stephania contains many bis-benzylisoquinoline-type compounds such as tetrandrine and fangchinoline.^{4,5} Tetrandrine is a principle compound and shown to be effective in experimental allergic encephalitis, airway micro vascular leakage, subcutaneous air pouch inflammation and adjuvant-induced chronic inflammation.^{6–9} It also inhibits precapillary formation of vascular endothelial cells and angiogenesis of cultured choroidal explants in STZ-diabetic rats.^{9,10} Fangchinoline and tetrandrine have similar inhibitory activities on angiotensin I converting enzyme,^{4,5} and induction of proinflammatory cytokines, interleukin-1 and tumor necrosis factor- α , by *Staphylococcus aureus* Cowan 1-stimulated human peripheral blood mononuclear cells.¹¹ In addition, these compounds show different actions on the anti-inflammation containing inhibition of cyclooxygenase and interleukin-5 activities although they are similar in chemical

structure.¹²

In the present study, effects of bis-benzylisoquinoline compounds containing fangchinoline and tetrandrine isolated from *Stephania* on the blood glucose level were investigated in the STZ-diabetic mice. An effect of *Astragali* on the action of fangchinoline was also investigated to confirm the combined effect of *Stephania* and *Astragali*. Finally, chemical structure–activity relationship of used *Stephania* compounds were clarified.

MATERIALS AND METHODS

Preparation of Streptozotocin-Diabetic Mice Fed male mice (ddY strain; 5 weeks of age; body weight, 22–25 g; Kiwa Laboratory Animal Science Co. Ltd., Wakayama, Japan) were injected with a single dose (150 mg/kg) of STZ (Sigma, St. Louis, MO, U.S.A.) in saline into the tail vein. STZ-induced diabetic mice (8–9 weeks of age; body weight, 22–46 g) were used for experiments 3–4 weeks after the injection. Age-matched normal male mice (ddY strain; 8–9 weeks of age; body weight, 29–42 g) were used in the control experiments. These mice were housed with PMI Laboratory Diet (Japan SLC, Sizuoka, Japan) and water *ad libitum* at 25–26 °C with lights on from 7 a.m. to 7 p.m. Drugs were administered into mice fasted from 8 p.m. to 10 a.m. The Ethics Review Committee for Animal Experimentation of Hokuriku University approved the experimental protocol.

Preparation and Administration of Drugs *Stephania* (*Stephania tetrandra* S. MOORE) and *Astragali* (*Astragalus membranaceus* Bunge) were collected from Anhui shen, China, during autumn and from Neimeng gu, China, during

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autumn, respectively. These crude drugs were extracted in 6 volumes of distilled water at 96–98 °C for 40 min with an automatic extractor "Torobi" (Tochimoto, Osaka Japan). Water extracts of these drugs were filtered through a mesh (No. 42, Sanpo, Tokyo, Japan), lyophilized with a freeze-drier (DF-03G, ULVAC, Tokyo), and stored at 4 °C. Dry weight yields of extracts of *Stephania* and *Astragalus* are 5.7 and 15.0% (w/w), respectively.³⁾ Tetrandrine (1(β)-6,6',7,12-tetramethoxy-2,2'-dimethyl berbaman) was purchased from Aldrich Chemicals Co. Ltd. (Milw., WI, U.S.A.). Fangchinoline, tetrandrine-2'-*N*- β -oxide (TD-7), tetrandrine 2'-*N*- α -oxide (TD-11), tetrandrine-2-*N*- β -oxide (TD-10), fangchinoline 2'-*N*- α -oxide (TD-8), 2'-*N*-norfangchinoline (TD-28), 2'-*N*-methyltetrandrinium chloride (TD-13), cycleanorine, cycleanine (TD-14), cyclanoline chloride and Stephenanthrine were obtained from Tsumura Co. Ltd., Tokyo. These chemical structures were summarized in Chart 1.^{4,5)} These extracts and compounds were suspended homogeneously in saline containing 1% Avicel (Asahi Chemical Industry, Tokyo), and administered intraperitoneally (i.p.: 0.1 ml/10 g body weight) into 14 h-fasted mice, respectively.

Measurement of Blood Glucose and Insulin Levels

Blood samples were collected from orbital vein plexus of mice and centrifuged at 3000 rpm at 4 °C for 20 min. Blood glucose levels of the supernatant were measured by the glucose oxidase method with a glucose B-test (Wako, Osaka) or Backman glucose analyzer (type II, Backman Coulter, Tokyo). Blood glucose levels were measured in fasted mice before, and 6 h after the administration of drugs, respectively. The fall % of blood glucose (BG) was calculated as $[\text{BG (before drug treatment)} - \text{BG (after drug treatment)}] / [\text{BG (before drug treatment)} - 85] \times 100$. Eighty-five are average of BG of 14 h-fasted normal mice.^{2,3)} Blood insulin level of 3 h-fasted mice was measured by the mouse ELISA kit for insulin (Morinaga, Yokohama, Japan).

Statistical Analyses All values were expressed as means \pm S.E.M. Differences between group data were evaluated by one-way analysis of variance followed by the multiple range test of Scheffé, or unpaired *t*-test at $p=0.05$ or 0.01. A value of $p<0.05$ was considered statistically significant.

RESULTS

Glucose and Insulin Levels in Blood of Streptozotocin-Diabetic Mice Blood glucose level in fed STZ-injected mice increased in a time dependent manner and became maximal on 12 d after the STZ-treatment (Fig. 1). The high level of blood glucose was kept up to 28 d after the STZ-treatment. The blood glucose levels in 14 h-fasted diabetic mice on 21 to 28 d after the STZ-treatment decreased to approximately 300 mg/dl but were sustained to the higher level than those of age-matched normal fasted mice (Fig. 1). Blood insulin levels in 3 h-fasted diabetic mice 21 d after STZ treatment were decreased to 22% of those in the age-matched normal mice (Fig. 1). The blood insulin levels in 3 h-fasted diabetic mice were not significantly different from the levels in 14 h-fasted diabetic mice (data not shown). From these results, the diabetic mice 21–28 d after the STZ-treatment were fasted for 14 h and used for the following experiments.

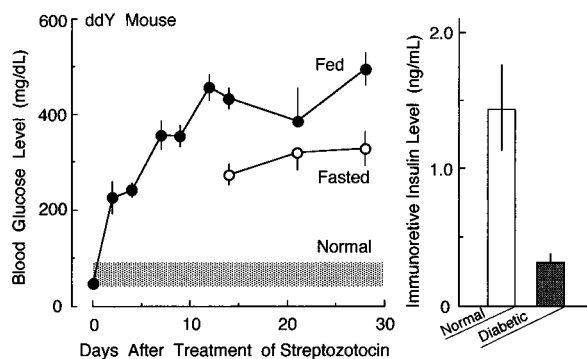


Fig. 1. Time-Dependent Increase in Blood Glucose Levels of Fed and Fasted STZ-Diabetic Mice (Left) and Blood Immunoreactive Insulin Levels in the STZ-Diabetic Mice (Right)

STZ (150 mg/kg) in saline was administered into tail vein of ddY male mice at 5 weeks of age. Blood glucose levels were measured in fed (●) and 14 h-fasted (○) STZ-diabetic ddY mice and age-matched normal mice with 14 h-fasting (shaded column) (left). Blood insulin levels were measured in 3 h-fasted mice 21 d after STZ administration (shaded column) and 3 h-fasted age-matched normal mice (open column) (right). Values are expressed as means \pm S.E.M. of 7–8 data (left) and 9 data (right). Shaded column in left panel represents the standard error of mean of data in age-matched normal mice.

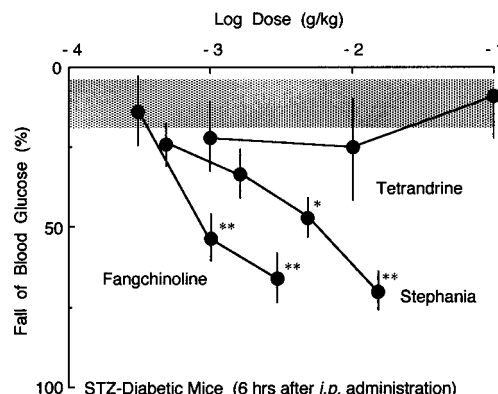


Fig. 2. Effects of Fangchinoline, Tetrandrine and Stephania on the Blood Glucose Levels in the STZ-Diabetic Mice

Blood glucose (BG) levels were measured before and 6 h after the administration of these drugs in 14 h-fasted diabetic mice. The fall % of blood glucose was calculated as $[\text{BG (before drug treatment)} - \text{BG (after drug treatment)}] / [\text{BG (before drug treatment)} - 85] \times 100$. Eighty-five are BG (mg/dl) of 14 h-fasted normal mice. The values are expressed as means \pm S.E.M. of 4–9 data. Shaded column represent standard error of mean of 13 data in the saline administration group. * $p<0.05$. ** $p<0.01$: Significantly different from the saline group.

Effects of Tetrandrine and Fangchinoline on Blood Glucose Level in the Diabetic Mice Effects of tetrandrine and fangchinoline on blood glucose level were compared with that of water extract of *Stephania* in the diabetic mice. Fangchinoline (0.3–3 mg/kg) as well as the water extract of *Stephania* (0.48–16 mg/kg) significantly fell high level of blood glucose in the diabetic mice in a dose-dependent manner. The anti-hyperglycemic effect of fangchinoline was significantly greater than that of the *Stephania* extract (Fig. 2).

However, tetrandrine (1–100 mg/kg) did not have a significant action on the blood glucose level compared with that of saline without drug (Fig. 2).

Combined Effect of Astragali on the Anti-hyperglycemic Action of Fangchinoline We have previously reported that *Astragalus* has the combined effect on the anti-hyperglycemic action of *Stephania*.³⁾ The present study was investigated effect of *Astragalus* on the anti-hyperglycemic action of fangchinoline. Fangchinoline did not have action at

0.3 mg/kg in shadowed part of Fig. 3A and in the lowest dose in Fig. 3B and increased anti-hyperglycemic action in a dose-dependent manner. The extract of Astragali (0.48–160 mg/kg) singly did not have a significant anti-hyperglycemic action in the diabetic mice compared with saline group without drugs (Fig. 3B). However Astragali (3–100 mg/kg) potentiated significantly the action of fangchinoline (0.3 mg/kg) in a dose-dependent manner (Fig. 3A). The effect of 30 mg/kg Astragali in the presence of fangchinoline (0.3 mg/kg) was similar to that of fangchinoline (1 mg/kg) without Astragali (Fig. 3).

Chemical Structure–Activity Relationships of Compounds Isolated from *Stephania* Anti-hyperglycemic ef-

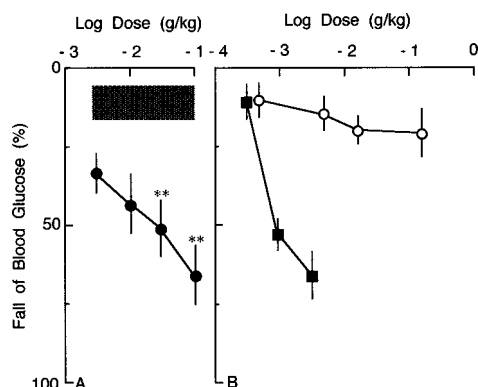


Fig. 3. Potentiating Effect of Astragali on the Anti-hyperglycemic Action of Fangchinoline in the STZ-Diabetic Mice

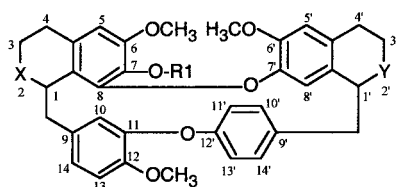
Blood glucose levels were measured before and 6 h after the administration of both various doses of Astragali and 0.3 mg/kg fangchinoline (A: ●), and Astragali (B: ○) and fangchinoline (B: ■) singly in 14 h-fasted diabetic mice. The fall % of blood glucose was calculated as described in the legend of Fig. 2. The values are expressed as means ± S.E.M. of 6–15 data. Shaded column in A represented standard error of mean of 15 data in single administration group of 0.3 mg/kg fangchinoline. ** $p < 0.01$: Significantly different from the group of single administration of fangchinoline.

fects of tetrandrine 2'-N-β-oxide (TD-7), tetrandrine 2'-N-α-oxide (TD-11), tetrandrine 2-N-β-oxide (TD-10), 2'-N-methyltetrandrinium chloride (TD-13), cycleanorine, fangchinoline 2'-N-α-oxide (TD-8), 2'-N-norfangchinoline (TD-28), cycleanine (TD-14), cyclanoline chloride and stephananthrine were compared with those of fangchinoline and tetrandrine in the STZ-diabetic mice. Fangchinoline, fangchinoline 2'-N-α-oxide (TD-8) and 2'-N-norfangchinoline (TD-28) (1 mg/kg) decreased significantly to near 50% of the high

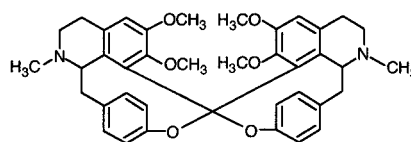
Table 1. Effects of Compounds Isolated from *Stephania* on the Blood Glucose Levels in the Diabetic Mice

Drugs	Fall of blood glucose	
	n	(%)
Saline	13	10.9 ± 7.7
Tetrandrine	5	22.2 ± 11.3
TD-7	4	53.5 ± 15.5*
TD-11	4	59.0 ± 10.7**
TD-10	7	48.2 ± 7.2**
TD-13	4	7.5 ± 10.1
Cycleanorine	6	20.2 ± 11.8
Fangchinoline	7	52.7 ± 6.7**
TD-8	4	50.7 ± 14.5*
TD-28	5	40.3 ± 11.1*
Cycleanine	6	50.1 ± 9.0**
Cyclanoline	7	24.0 ± 8.8
Stephananthrine	7	7.4 ± 15.4

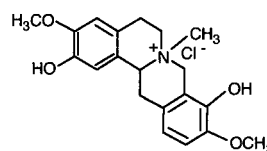
Blood glucose levels were measured before and 6 h after the administration of saline, tetrandrine, tetrandrine-2'-N-β-oxide (TD-7), tetrandrine 2'-N-α-oxide (TD-11), tetrandrine-2-N-β-oxide (TD-10), 2'-N-methyltetrandrinium chloride (TD-13), cycleanorine, fangchinoline, fangchinoline 2'-N-α-oxide (TD-8), 2'-N-norfangchinoline (TD-28), cycleanine, cyclanoline chloride and stephananthrine (1 mg/kg) in 14 h-fasted diabetic mice. The fall % of blood glucose was calculated as described in the legend of Fig. 2. The values are expressed as means ± S.E.M. of 4–13 data. n represents number of data. * $p < 0.05$, ** $p < 0.01$: Significantly different from the value of saline alone by unpaired t-test.



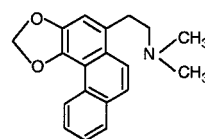
Compounds	R1	X	Y
Fangchinoline	H	N-CH ₃	N-CH ₃
Tetrandrine	CH ₃	N-CH ₃	N-CH ₃
Tetrandrine 2'-N-β-oxide (TD-7)	CH ₃	N-CH ₃	N-CH ₃ ↓ O
Tetrandrine 2'-N-α-oxide (TD-11)	CH ₃	N-CH ₃	N-CH ₃ ↓ O
Tetrandrine 2-N-β-oxide (TD-10)	CH ₃	N-CH ₃ ↓ O	N-CH ₃
Fangchinoline 2'-N-α-oxide (TD-8)	H	N-CH ₃	N-CH ₃ ↓ O
2'-N-Norfangchinoline (TD-28)	H	N-CH ₃	NH
2'-N-Methyltetrandrinium chloride (TD-13)	CH ₃	N-CH ₃	N ⁺ -CH ₃ Cl ⁻ CH ₃
Cycleanorine	CH ₃	N-CH ₃	NH



Cycleanine (TD-14)



Cyclanoline chloride



Stephananthrine

Chart 1. Chemical Structures of Used Alkaloids Isolated from *Stephania*

blood glucose level in the diabetic mice (Table 1). However, tetrandrine, 2'-*N*-methyltetrandrinium chloride (TD-13) and cycleanorine (1 mg/kg) did not affect the high blood glucose level. In addition, tetrandrine 2'-*N*- β -oxide (TD-7), tetrandrine 2'-*N*- α -oxide (TD-11), tetrandrine 2-*N*- β -oxide (TD-10), fangchinoline 2'-*N*- α -oxide (TD-8) (1 mg/kg) also significantly decreased to near 50% of the high blood glucose level. Cycleanine (1 mg/kg), which has head to tail ether bonds, had also significant anti-hyperglycemic effect. However, cyclanoline chloride and stephananthrine (1 mg/kg), which do not have a bis-benzylisopiquinoline structure, did not affect the blood glucose level (Table 1).

DISCUSSION

We have previously reported that Kampo medicine, Boi-ogi-to, increases blood insulin level and falls high level of blood glucose in the STZ-diabetic mice. The water extract of *Stephania*, but not *Sinomeni Caulis* ET *Rhizoma* in Boi-ogi-to shows increase in blood insulin release and anti-hyperglycemic action.^{2,3)} The present study demonstrates that fangchinoline, a main bis-benzylisoquinoline compound in *Stephania* had a potent anti-hyperglycemic action in the STZ-diabetic mice. Fifty% inhibitory dose of fangchinoline with 95% confident limit was 1.23 mg/kg (0.81—1.89) and significantly smaller than the dose of *Stephania* extract [4.77 mg/kg (2.59—8.80)]. The potency of fangchinoline was 3.9-fold greater than that of *Stephania* extract. However, tetrandrine, another main bis-benzylisoquinoline compound, did not have such an anti-hyperglycemic action in the diabetic mice. These results demonstrate that fangchinoline but not tetrandrine has a role for these actions of *Stephania* in Boi-ogi-to.

Fangchinoline and tetrandrine are reported to have similar inhibitory effects on the experimental thrombosis induced by collagen and epinephrine,¹³⁾ human polymorphonuclear leukocyte function,¹⁴⁾ human platelet aggregation and thromboxane B₂ formation,¹⁵⁾ the activity on angiotensin I converting enzyme,^{4,5)} and the induction of proinflammatory cytokines, interleukin-1 and tumor necrosis factor- α .¹¹⁾ These results indicate that the active moiety of fangchinoline is similar to that of tetrandrine for these actions. On the other hand, fangchinoline and tetrandrine have different effects on the activities of cyclooxygenase and interleukin-5. Fangchinoline inhibits the activity of cyclooxygenase but tetrandrine does not show any inhibition.¹²⁾ The present results also demonstrate that fangchinoline but not tetrandrine fell the high level of blood glucose in the diabetic mice, indicating that the active moiety of fangchinoline differs from that of tetrandrine in the falling action on blood glucose level. Pretreated tetrandrine has been reported to protect beta cells from injury induced by 5 h-exposed alloxan.¹⁶⁾ But, tetrandrine did not influence the higher blood glucose of STZ-diabetic mice 21 d after STZ injection. On the other hand, tetrandrine inhibits the angiogenesis of cultured choroidal capillary in the STZ-diabetic rat¹⁰⁾ and activation of NF- κ B in rat alveolar macrophages.¹⁷⁾ The diabetic state-induced choroidal angiogenesis may be associated with the angiogenic action of N^ε-(carboxy methyl)lysine (CML), a major advanced glycation end product (AGE) in the diabetic rat.¹⁸⁾ These results suggest that *Stephania* may have several

actions during the course of diabetes such as anti-hyperglycemic action of fangchinoline and improving actions of tetrandrine on the mechanisms linking hyperglycemia with tissue damage such as the mechanism of AGEs in the diabetic complication.

We have previously reported that *Astragal* does not have direct effect but potentiates both insulin-releasing action and anti-hyperglycemic action of *Stephania* in the STZ-diabetic mice.³⁾ The present study confirms that *Astragal* significantly potentiated the anti-hyperglycemic action of fangchinoline in *Stephania*. Effect of 30 mg/kg *Astragal* in the presence of 0.3 mg/kg fangchinoline was similar to the effect of 1 mg/kg fangchinoline alone, indicating that *Astragal* potentiates the action of fangchinoline to a 3-fold greater extent. Some components in *Astragal* extract may potentiate insulin-releasing action and anti-hyperglycemic action of fangchinoline, although we do not have a direct evidence for actions of fangchinoline on insulin release yet. Mechanisms of combined action of *Astragal* components and fangchinoline are unknown at the present time. The details need to be further investigated on their combined effects on insulin release in the diabetic mice.

Anti-hyperglycemic actions of used compounds isolated from *Stephania* were compared. Tetrandrine 2'-*N*- β -oxide (TD-7), tetrandrine 2'-*N*- α -oxide (TD-11), tetrandrine 2-*N*- β -oxide (TD-10), fangchinoline 2'-*N*- α -oxide (TD-8), 2'-*N*-norfangchinoline (TD-28) and cycleanine had similar anti-hyperglycemic actions as fangchinoline did in the diabetic mice. The yields of these compounds in the water extract of *Stephania* are estimated to be 0.22% (fangchinoline), 0.0062% (tetrandrine 2'-*N*- β -oxide; TD-7), 0.0065% (tetrandrine 2'-*N*- α -oxide; TD-11), 0.0014% (tetrandrine 2-*N*- β -oxide; TD-10), 0.00059% (fangchinoline 2'-*N*- α -oxide; TD-8) and 0.00066% (cycleanine), respectively.^{4,5)} Since the effects of these compounds did not recover completely the effect of *Stephania* extract, these compounds and other compounds might interact synergistically in the anti-hyperglycemic action of *Stephania* extract.

Relation of chemical structures with anti-hyperglycemic activity was investigated using these anti-hyperglycemic alkaloids in *Stephania*. Fangchinoline, fangchinoline 2'-*N*- α -oxide (TD-8) and 2'-*N*-norfangchinoline (TD-28), which substituted with a 7-hydroxy side chain, had similar anti-hyperglycemic actions to each other. But tetrandrine, 2'-*N*-methyl tetrandrinium chloride (TD-13) and cycleanorine, which have a structure of 7-*O*-methyl, did not affect the blood glucose level. These results demonstrate that the demethylation at the 7-*O* position in these compounds is essential for their anti-hyperglycemic actions. In addition, tetrandrine 2'-*N*- β -oxide (TD-7), tetrandrine 2'-*N*- α -oxide (TD-11), tetrandrine 2-*N*- β -oxide (TD-10), fangchinoline 2'-*N*- α -oxide (TD-8), which are added to side chain of 2- or 2'-*N*-oxide, showed significant anti-hyperglycemic actions. But tetrandrine, 2'-*N*-methyltetrandrinium chloride (TD-13) and cycleanorine, which have 2- and/or 2'-*N*-methyl side chain, had no effect. From these results, the 2- or 2'-*N*-oxide added to tetrandrine as well as the demethylation at the 7-*O* position have an important role for their anti-hyperglycemic actions. Fangchinoline 2'-*N*- α -oxide (TD-8), which has both 7-hydroxy and 2'-*N*-oxide side chains, did not increase the anti-hyperglycemic action of fangchinoline. The result suggests

that one of demethylation of 7-O position and addition of 2- or 2'-*N*-oxide has a role for the induction of anti-hyperglycemic action.

It is reported that anti-hypertensive effect of tetrandrine is attenuated by the demethylation at the 7-O position and the substitution of *N*-methyl groups at the 2- and 2'-position with *N*-oxide, indicating that the anti-hypertensive moieties of tetrandrine are 7-*O*-methyl group and *N*-methyl group at the 2- and 2'-positions.¹⁹⁾ The active moieties of tetrandrine-derivatives for the anti-angiogenic activity in the diabetic choroidal capillary are reported to be the bis[tetrahydroisoquinoline] moiety connected by oxy-bis[phenylenemethylene] and 2,2'-*N*-methyl group.¹⁰⁾ These different active moieties of bis-benzylisoquinoline compounds in *Stephania* interact with different sites of action for the anti-hyperglycemic and anti-angiogenic effects during the course of diabetes.

In conclusion, fangchinoline, but not tetrandrine in *Stephania* had a potent anti-hyperglycemic action in STZ-diabetic mice. From the chemical structure-activity relation of *Stephania* compounds, the demethylation at the 7-O position and/or addition of 2- or 2'-*N*-oxide side chains in these bis-benzyl-isoquinoline compounds have a role for the induction of anti-hyperglycemic action in the diabetic mice.

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