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Original Article

Antihyperglycemic Effect of Silkworm Powder, Fibroin and Sericin from Three Thai Silkworm (*Bombyx mori* Linn.) in Streptozotocin-Induced Diabetic Rats

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ABSTRACT

Objective: The present study was aimed to investigate the antihyperglycemic activities of Thai silkworm (*Bombyx mori* Linn.) powder, fibroin and sericin from three races of Thai silkworm including Nangnoi, Nanglai, and Samrong in streptozotocin-induced diabetic rats. **Materials and Methods:** All rats were daily and orally administered with silkworm powder (5th-instar, 3rd-day), fibroin, and sericin at a dose of 250 mg/kg for 6 weeks. After that, various parameters including body weight, blood glucose, hematological and biochemical parameters were determined. **Results:** The results revealed that fasting plasma glucose level in 6th week of Nanglai fibroin, Nangnoi fibroin and Nangnoi sericin expressed a better reduction of FPG in diabetic rats compared with diabetic control groups ($p<0.05$). All hematological parameters of each group were not different within those values ($p>0.05$). In case of blood urea nitrogen, creatinine and alkaline phosphatase value showed that some of treated groups was different from diabetic control ($p<0.05$), while all of treated groups showed different in cholesterol and high density lipoprotein value ($p<0.05$). **Conclusion:** Silkworm powders, fibroin and sericin of three races exhibited a therapeutic potential for the reduction plasma glucose level. Treatments of silkworm powder, fibroin and sericin did not have any effect on hematological parameters. Improvement of blood urea nitrogen, creatinine, alkaline phosphatase values and lipid profiles also were also observed in the treatment groups.

Key words: Antihyperglycemic effect, Diabetic rats, Silkworm, Sericin, Fibroin.

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INTRODUCTION

The silkworm was domesticated from the wild silk moth, *Bombyx mandarina*. The domesticated *B. mori* and the wild *B. mandarina* can still breed and sometimes produce hybrids.[1] Silkworms have been bred to produce raw silk in China for thousands of years from where it spread to Korea and Japan, and later to India and the West.[2] Mulberry silkworm (*B. mori*) has been reared for longtime in many regions of Thailand especially the Northeast.[3] Reports on the various pharmacological activities of the silkworm have been accumulated such as antioxidant,[4] anticancer,[5] antibacterial,[6] antiviral,[7] antihypertensive,[8] and hepatoprotective activities.[9]

Type 2 diabetes is a chronic disease with the mechanisms potentially linked to overweight and obesity. In the year 2014, the prevalence of diabetes was approximately 9% worldwide. It is particularly caused of disability, premature death and increasing the risk of several chronic diseases such as cardiovascular diseases and renal failure.[10] Novel therapeutic agents are urgently needed for prevention or treatment.[11] The use of natural products is considerably one of the choices to prevent the disease. The non-sericin component from silkworm cocoon exhibited an effective *in vivo* reduction of blood glucose in streptozocin-induced diabetes mice.[12] The antidiabetic activity was possibly related to α-glucosidase inhibitory effect, which had been identified as functions of 1-deoxynojrimycin.[13]

In Thailand, there are several varieties of native silkworm races traditionally reared household or as wild types. The difference of races was provided different pharmacological capacities.[4] Fibroin and sericin from silkworm were generally used as medical biomaterial.[14] However, there is no report regarding comparison of silkworm powder, fibroin and sericin in *in vivo* antidiabetic activity. Therefore, the purposes of this study was to compare hypoglycemic activity of silkworm powder, fibroin and sericin from three Thai mulberry silkworm races as well as investigation of the hematological and biochemical parameters in STZ-induced diabetic rats after oral administration of silkworm powder (5th-instar, 3rd-day), fibroin, and sericin.

MATERIALS AND METHODS

Animals

Male albino Wistar rats, aged 5 to 7 weeks with body weight of 180-200 g were used.[15] These animals were

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purchased from National Laboratory Animal Center, Mahidol University, Thailand. The rats were fed with a standard diet from National Laboratory Animal Center (Nakhon Prathom, Thailand), and allowed to access to water *ad libitum*, and acclimated to laboratory conditions for 7 days. All rats were kept in separate cages. One control and one diabetic rat were kept in the same cage. They were provided with feed and water daily for up to 6 weeks until used in the study. All groups were kept in a temperature-controlled room (23 ± 2 ºC), artificially lit from 6.00 to 18.00 hours daily.[16] The body weights and blood glucose levels of the rats were recorded weekly. The experimental procedure was performed in accordance with the advice of the Institutional Animal Care and Use Ethic Committee, Mahasarakham University, Thailand (Approval license No. 0015/2011).

Induction of diabetes in rats

The initial blood glucose levels of rats were measured using an Accu-Check® active testing kit. The blood was taken from the tail vein.[17] The bodyweight was also measured to investigate the change in body weight over the six weeks. In order to induce diabetes, streptozotocin (STZ) at dose of 65 mg/kg bodyweight (b.w.) was injected intraperitoneally to the rats with a single injection. Streptozotocin was freshly dissolved in 20 mM citrate buffer at pH 4.5. The control rats were injected with 20 mM citrate buffer (pH 4.5) at an equivalent volume to the diabetic group. To avoid the initial hypoglycemic mortality, 2% sucrose was prepared as drinking water for the STZ-induced diabetic rats for 48 hours.[18] At the 7th day, the blood glucose of each rat was measured after overnight fasting for 12 hours. The blood glucose level in control rats should be lower than 100 mg/dL. For diabetic groups, the blood glucose level of 126 mg/dL or higher was recruited into the study.

Preparation of silkworm powder

Three varieties of Thai mulberry silkworms including Nangnoi (NN), Nanglai (NL), and Samrong (SR) were reared at Silk Innovation Center, Mahasarakham University, Thailand. Identification of silkworm races was performed with regard to the Queen Sirikit Department of Sericulture protocol. The 5th instar, 3rd day silk larvae were used to prepare silkworm powder according to the study of Ryu *et al.*[19] suggesting that the highest bioactive compounds were found in this life stage of mulberry silkworm. The silkworms were then freeze-dried and ground in order to obtain fine powders. Silkworm powders were kept in freezer before use.

Preparation of fibroin and sericin

Silkworms (*B. mori*), from Nanglai, Nangnoi and Samrong races from Silk Innovation center Mahasarakham University, Thailand, producing yellow cocoons were reared. The extraction and separation of sericin and fibroin were performed in accordance with Martínez-Mora *et al.*[20] After the cocoon was formed, pupae were extracted. The empty cocoons were then boiled twice for 45 min in 0.02 M Na_2CO_3. The solution containing sericin fraction was dialyzed for three days in deionized water with a 3,500 molecular weight cut-off membrane. The remaining fibroin was separated from sericin solution by filtration. To obtain a high purity fibroin, the fibroin was rinsed thoroughly with large amount of water to clean the remaining sericin proteins. The fibroin was then dried at room temperature for 72 h and dissolved in 9.3 M LiBr for 3hours at 60°C to generate a 20% w/v solution. Then, the solution was further dialyzed in distilled water for 3 days and the resultant solution was freeze-dried and stored at 4°C. To obtain the desired concentration, the purified silk fibroin was dissolved in deionized water. According, the method proposed by Martínez-Mora *et al.*,[20] the purity of sericin and fibroin were approximately 99%.

Experimental designs

The animals were randomly divided into the following twelve experimental groups with 6 animals in each: group 1 was normal control rats treated orally with distilled water; group 2 was diabetic control rats treated orally with distilled water; group 3 was treated with glibenclamide (0.25 mg/kg b.w.); group 4-6 were diabetic rats treated orally with silkworm powder (250 mg/kg b.w.) of Nanglai (NL-W), Nangnoi (NN-W), and Samrong (SR-W) races, respectively; group 7-9 were diabetic rats treated orally with fibroin (250 mg/kg b.w.) of Nanglai (NL-F), Nangnoi (NN-F), and Samrong (SR-F) races, respectively; group 10-12 were diabetic rats treated orally with sericin (250 mg/kg b.w.) of Nanglai (NL-S), Nangnoi (NN-S), and Samrong (SR-S) races, respectively. Silkworm powder and glibenclamide were suspended in 1% carboxymethyl cellulose and orally administered using orogastric tube dialy at 10 a.m. for 6 weeks.

Effect of silkworm powder, fibroin, and sericin on body weight

The normal and STZ-induced diabetic rats were weighed weekly before silkworm or water administration to investigate the change of body weight during 6 weeks of the experiment.

Effect of silkworm powder, fibroin, and sericin on fasting plasma glucose levels

The normal and STZ-induced diabetic rats were fasted for 12 hours. Then, the blood samples were collected from the tail vein of each rat and measured plasma glucose by using Accu-check® Advantage II (Roche, Germany). FPG were measured every 2 weeks in each experimental group.

Effect of silkworm powder, fibroin, and sericin on hematological and biochemical parameters

Sixth weeks after the experiments, all rats were fasted for 12 hours. They were sacrificed by cervical dislocation technique. Then, blood samples obtained from cardiac puncture[21] were analyzed for hematological values including red blood cell counts (RBC), white blood cell counts (WBC), % of hematocrit (Hct) and g % of hemoglobin (Hb), and biochemical parameters including total cholesterol (CHO), triglyceride (TG), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), blood urea nitrogen (BUN), creatinine, and alkaline phosphatase (ALP) by an automatic blood chemical analyzer (BT 2000 plus, Germany).

Statistical analysis

All data were expressed as mean ± standard error of mean (S.E.M.). Statistical analysis was carried out using *F*-test (One-way ANOVA) followed by Scheffe's test using SPSS version 15. The statistical significant difference was obtained at a *p*-value less than 0.05.

RESULTS AND DISCUSSION

Effect of silkworm powder, fibroin, and sericin on body weight

Silkworm powder from three races of Thai silkworm (NL, NN, and SR) increased the body weight of rats in all treatments throughout six weeks of the experiments. However, diabetic control rats have slightly decrease body weight (**figure 1**). Interestingly, diabetic rats treated with glibenclamide have remarkably increased body weight throughout six weeks of the experiment, almost equivalent to those from normal control rats, suggesting the efficacy of glibenclamide in recovering the severity of the disease. On the other words, diabetic rats treated with the three races of silkworm powder, fibroin and sericin tended to have slightly increased

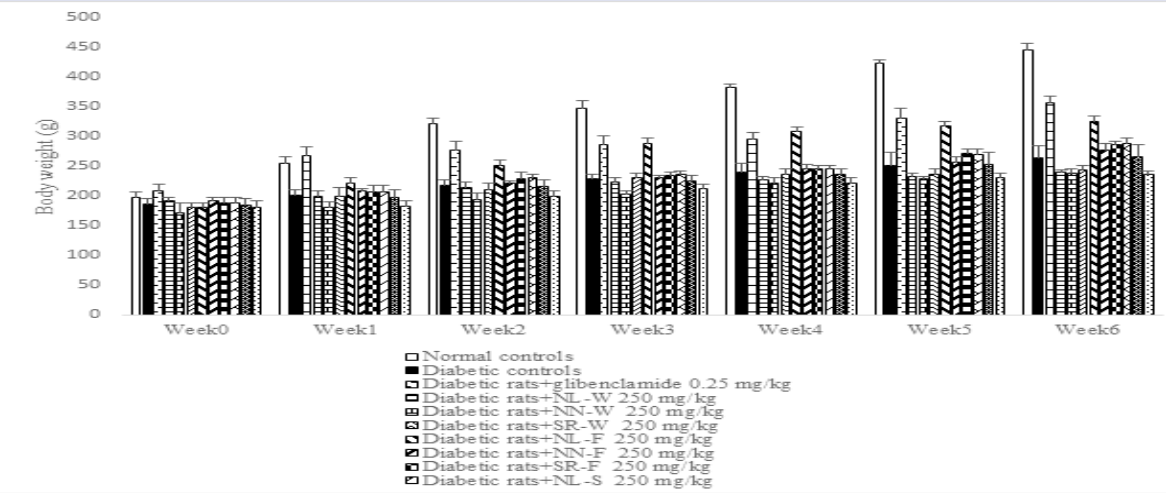

Figure 1: Body weight of normal control, diabetic control, and diabetic rats treated with glibenclamide, silkworm powder, fibroin and sericin of three silkworm races.

body weight. The body weight loss could be from glycolysis, lipid and protein metabolism in muscle in order to get sufficient energy, which causes by insulin-mediated glucose uptake resistance of peripheral tissues to utilize glucose as a primary energy source.[22] For this reason, diabetic rats showed lower body weight comparing with normal rats.

Effect of silkworm powder, fibroin, and sericin on fasting plasma glucose levels

As shown in **Table 1**, lowering FPG effect in normal rats and diabetic rats which treated with silkworm powder, fibroin and sericin of three varieties at dose of 250 mg/kg b.w. and glibenclamide were observed for 6 weeks. The finding presented significantly decreased FPG in some week. Decreasing of FPG in those silkworms compared to normal rats and diabetic rats started from initial time were almost equal to glibenclamide (0.25 mg/kg b.w.) treatment group; particularly at the second week for Nanglai fibroin and Nangnoi fibroin treatment had better reduction of FPG than glibenclamide and others, whereas Nanglai fibroin, Nangnoi fibroin, Nangnoi sericin and glibenclamide groups appeared decreasing FPG at sixth week. The antihyperglycemic activities of silkworm powders were previously explained by Kiyotaka *et al.*[23] that silkworm powder has high 1-deoxynojirimycin (DNJ) contents about 0.3% w/w. DNJ was a well-known in alpha-glucosidase inhibitory activity.[24] In addition, other chemical compositions in silkworm powder such as beta-sitosterol and stigmasterol has been reported on antidiabetic activity in STZ-induced diabetic rat.[25-26] Regarding other compounds, the silk protein (1:1 of fibroin and sericin) fed mice showed significantly lower insulin level and higher glycogen concentration than the high fat-fed mice.[27] Previous studies on silk protein pointed out that the soluble fibroin could decrease blood glucose and increase insulin concentrations in mice.[28-29] Similar effect had been observed by Okazaki *et al.*[30] that dietary feeding of silk sericin decreased in plasma glucose and increased insulin secretion after an interperitoneal glucose injection in high fat-fed rats.

Table 1: FPG of normal control, diabetic control, diabetic rats treated with glibenclamide, silkworm powder, fibroin and sericin of three silkworm races.

treatments	FPG (mg/dL)			
	week0	week2	week4	week6
Normal control	79.16±5.18*	93.50±6.11*	98.50±5.81*	107.33±5.38*
Diabetic control	200.03±16.91	492.33±41.69	528.33±44.75	519.50±43.91
Diabetic rats+glibenclamide 0.25 mg/kg	219.17±9.64	232.50±10.16	115.50±5.17*	79.33±3.48*
Diabetic rats+NL-W 250 mg/kg	246.32±10.31	239.13±21.68	387.61±21.35	388.62±16.71
Diabetic rats+NN-W 250 mg/kg	234.50±9.53	238.90±17.11	305.50±12.78	388.51±20.45
Diabetic rats+SR-W 250 mg/kg	274.17±12.19	332.54±19.53	404.31±10.17	476.35±21.19
Diabetic rats+NL-F 250 mg/kg	164.50±10.08	98.50±6.20*	79.50±4.85*	81.50±5.12*
Diabetic rats+NN-F 250 mg/kg	131.16±5.13	79.33±4.40*	65.50±4.07*	89.67±4.67*
Diabetic rats+SR-F 250 mg/kg	132.50±8.75	198.50±19.38	416.66±15.47	271.66±21.19
Diabetic rats+NL-S 250 mg/kg	195.02±15.54	209.66±16.70	342.33±27.33	210.50±16.97
Diabetic rats+NN-S 250 mg/kg	158.33±12.49	162.50±4.96	102.50±8.12*	103.66±8.14*
Diabetic rats+SR-S 250 mg/kg	195.03±14.54	360.66±28.77	492.50±39.39	460.33±36.73

Data are shown as mean±S.E.M., (n=6). * showed significantly difference from diabetes control group ($p<0.05$).

Table 2: Hematological parameters of normal control, diabetic control, diabetic rats treated with glibenclamide, silkworm powder, fibroin and sericin of three silkworm races after 6 weeks treatment.

treatments	Hb (g%)	Hct (%)	RBC (10^6 cells/mL)	WBC (10^3 cells/mL)	Platelet (10^5 cells/mL)
Normal control	16.16±1.04	48.66±1.52	8.26±0.21	4.63±0.50	7.29±0.33
Diabetic control	17.03±0.97	50.66±3.78	8.70±0.40	4.83±1.09	7.64±0.91
Diabetic rats+glibenclamide 0.25 mg/kg	15.96±0.55	47.33±1.52	8.10±0.75	5.40±1.83	7.21±1.70
Diabetic rats+NL-W 250 mg/kg	15.56±1.72	47.33±4.50	8.50±0.95	5.63±0.40	6.66±0.08
Diabetic rats+NN-W 250 mg/kg	16.16±1.05	48.00±3.60	8.56±1.09	6.30±1.41	6.59±0.49
Diabetic rats+SR-W 250 mg/kg	16.83±0.72	50.66±2.51	8.93±0.58	4.83±0.40	6.49±0.32
Diabetic rats+NL-F 250 mg/kg	15.30±0.95	45.67±3.51	8.20±0.99	3.93±0.57	6.54±0.14
Diabetic rats+NN-F 250 mg/kg	17.73±1.36	52.66±4.04	8.10±0.75	4.33±1.33	6.79±0.94
Diabetic rats+SR-F 250 mg/kg	17.96±1.80	53.66±5.03	9.40±0.98	4.33±2.50	6.60±0.65
Diabetic rats+NL-S 250 mg/kg	15.73±2.43	47.33±6.65	8.33±0.86	4.60±1.90	6.82±0.97
Diabetic rats+NN-S 250 mg/kg	15.56±2.30	46.33±6.50	7.43±1.04	4.66±2.04	7.30±0.39
Diabetic rats+SR-S 250 mg/kg	16.53±1.89	49.33±5.68	8.60±1.32	4.26±2.02	7.24±0.48

Data are shown as mean± S.E.M. (n = 6).

Table 3: Blood chemical parameters (BUN, creatinine and ALP) of normal control, diabetic control, diabetic rats treated with glibenclamide, silkworm powder, fibroin and sericin of three silkworm races after 6 weeks treatment.

Treatment	BUN (mg/dL)	Creatinine(mg/dL)	ALP (IU/L)
Normal control	29.96±1.01*	0.90±0.10*	91.33±6.02*
Diabetic control	51.36±2.56	1.36±0.30	324.33±46.23
Diabetic rats+glibenclamide 0.25 mg/kg	39.56±3.91*	1.06±0.11*	93.66±9.21*
Diabetic rats+NL-W 250 mg/kg	38.66±3.74*	1.10±0.20*	247.33±26.02
Diabetic rats+NN-W 250 mg/kg	42.33±2.44*	1.10±0.10*	314.33±49.03
Diabetic rats+SR-W 250 mg/kg	49.46±6.50	1.33±0.15	169.00±27.07*
Diabetic rats+NL-F 250 mg/kg	40.73±5.77*	1.16±0.15*	77.33±4.72*
Diabetic rats+NN-F 250 mg/kg	39.63±5.52*	1.00±0.10*	126.00±19.97*
Diabetic rats+SR-F 250 mg/kg	39.70±4.34*	1.10±0.10*	192.67±29.70*
Diabetic rats+NL-S 250 mg/kg	47.36±6.83	1.20±0.30	92.00±2.64*
Diabetic rats+NN-S 250 mg/kg	37.96±3.80#	1.23±0.11	172.66±35.55*
Diabetic rats+SR-S 250 mg/kg	40.43±5.45#	1.30±0.31	212.66±13.05*

Data are shown as mean± S.E.M. (n=6). * showed significantly difference from diabetic controls group (p<0.05).

Table 4: Lipid profile (CHO, TG, HDL and LDL) of normal control, diabetic control, diabetic rats treated with glibenclamide, silkworm powder, fibroin and sericin of three silkworm races after 6 weeks treatment.

	Lipid profiles (mg/dL)			
Treatment	CHO	TG	HDL	LDL
Normal control	91.33±6.02*	119.33±14.57*	56.66±4.50*	57.00±5.56*
Diabetic control	292.00±58.59	285.66±11.59	24.33±4.50	113.66±3.05
Diabetic rats+glibenclamide 0.25 mg/kg	125.66±12.01*	151.00±25.35*	33.33±3.51*	76.33±3.05*
Diabetic rats+NL-W 250 mg/kg	183.66±13.31*	224.33±23.75	31.33±5.03*	77.00±9.16*
Diabetic rats+NN-W 250 mg/kg	185.66±40.41*	156.66±7.09*	39.33±2.51*	80.33±8.62*
Diabetic rats+SR-W 250 mg/kg	172.66±12.74*	183.33±8.50*	37.66±2.51*	107.00±5.56
Diabetic rats+NL-F 250 mg/kg	115.66±23.79*	175.33±22.81*	33.00±3.46*	74.33±7.50*
Diabetic rats+NN-F 250 mg/kg	129.00±15.52*	145.33±11.01*	32.66±5.50*	81.00±4.00*
Diabetic rats+SR-F 250 mg/kg	148.00±35.79*	118.33±15.17*	32.66±3.21*	78.00±3.52*
Diabetic rats+NL-S 250 mg/kg	191.66±16.25*	181.00±48.38*	41.33±8.32*	104.00±8.18
Diabetic rats+NN-S 250 mg/kg	150.00±32.14*	138.33±37.89*	35.00±5.56*	88.00±9.97*
Diabetic rats+SR-S 250 mg/kg	163.66±18.55*	215.00±43.00	37.66±1.15*	102.33±8.08

Data are shown as mean± S.E.M. (n=6). * showed significantly difference from diabetic control group (p<0.05).

Effect of silkworm powder, fibroin, and sericin on hematological data

Hematological parameters in rats from all treatments were investigated. These found that hemaglobin (Hb), red blood cell count (RBC), white blood cell count (WBC), and platelets values were not significantly difference (p>0.05) within those groups (**Table 2**). This study was the first report regarding toxicity of silkworm powder, fibroin and sericin on hematological parameters. In silkworm powder, the nutritional value of silkworm powder (5th instar and 3rd day) consisted of protein containing 16-18 amino acid about 60-70%.[14,31] The content of silkworm powder is not different from normal food. Therefore, changes in hematological parameters were not significant difference. Moreover, Kaskoos *et al*.[32] reported that the chemical compositions of the silkworm such as polyphenols did not effect on hematological parameters as well.

Effect of silkworm powder, fibroin, and sericin on renal and hepatic functions

The effects of all treatment groups on renal functions were expressed as BUN and creatinine values (**Table 3**). The most treatment groups showed that BUN values were significantly lower comparing with diabetic controls group (p<0.05). However, diabetic rats treated with Samrong silkworm and Nanglai silkworm were not significant difference from diabetic controls group (p>0.05). Regarding creatinine values, diabetic rats treated with Samrong silkworm, Nanglai sericin, Nangnoi sericin and Samrong sericin were not significant difference from diabetic controls group (p>0.05). However, other experimental groups were significantly different from diabetic control group (p<0.05). The previous study showed that silkworm containing quercetin improved BUN and creatinine values in rat.[33]

The effects of silkworm powder, fibroin and sericin on hepatic function were expressed as ALP (**Table 3**). The diabetic rats treated with Nanglai silkworm and Nangnoi silkworm were not significant different in ALP from diabetic controls group (p>0.05). However, other groups showed the lower ALP value compared with diabetic controls group (p<0.05).

Effect of silkworm powder, fibroin, and sericin on lipid profiles

The effect of all treatment groups on lipid profiles (CHO, TG, HDL and LDL) have been shown in **Table 4**. CHO and HDL values in all experimental groups were significant different from diabetic control group (p<0.05), while TG values in the most of experimental groups were significant different from diabetic control group (p<0.05). However, diabetic rats treated with Nanglai silkworm and Samrong sericin were not significant different from diabetic control group (p>0.05). LDL values in diabetic rats treated with Samrong silkworm, Nanglai sericin and Samrong ssericin were not significantly different from diabetic control group (p>0.05), while other groups were significant different (p<0.05). It can be explained that the decreasing of total cholesterol was possible from silk protein.[34] This study confirmed that silkworm, fibroin and sericin from Thai races had reduced complications by improving blood chemical parameters and blood lipid profiles in streptozotocin-induced diabetic rats.

CONCLUSION

Silkworm powders, fibroin and sericin of three races exhibited a therapeutic potential for the reduction plasma glucose level. Treatments of silkworm powder, fibroin and sericin did not have any effect on hematological parameters. Improvement of BUN, creatinine, ALP and lipid profiles also were also observed in the treatment groups.

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CONFLICT OF INTEREST

Authors declare no conflict of interest.

ABBREVIATIONS USED

FPG: fasting blood glucose level; **Hb:** hemoglobin; **Hct:** hematocrit; **RBC:** red blood cell; **WBC:** white blood cell; **BUN:** blood urea nitrogen; **ALP:** alkalinephosphatase; **CHO:** cholesterol; **TG:** triglyceride; **HDL:** high density lipoprotein; **LDL:** Low density lipoprotein; **NL:** Nanglai race; **NN:** Nangnoi race; **SR:** Samrong race; **W:** silkworm; **F:** fibroin; **S:** sericin.

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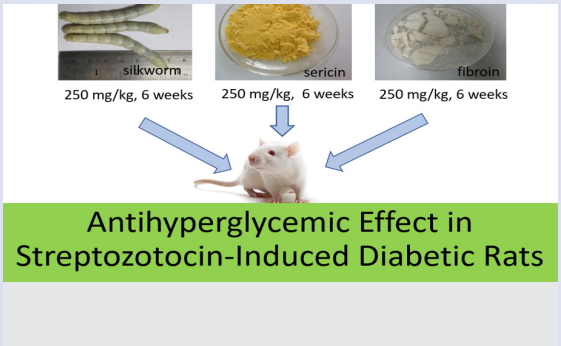
GRAPHICAL ABSTRACT



HIGHLIGHTS OF PAPER

- Silkworm (Bombyx mori L.) have been employed in traditional medicine in treatment for diabetes mellitus.
- Silkworm powder, fibroin and sericin, derived from silkworm have been used.
- The present study was aimed to investigate the antihyperglycemic activities of Thai silkworm (Bombyx mori L.) powder, fibroin and sericin of three races
- Silkworm powders, fibroin and sericin of three races exhibited a therapeutic potential for the reduction plasma glucose level. According hematological parameters, they expressed no effect on hematological parameters. Improvement of BUN, creatinine, ALP and lipid profiles also were also observed in the treatment groups

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