Int. J. Indust. Entomol. Vol. 4, No. 2, 2002, pp. 93~100

Review

International Journal of *Industrial Entomology*

Effects and Mechanisms of Silkworm Powder as a Blood Glucose-Lowering Agent

Kang Sun Ryu*, Heui Sam Lee and Iksoo Kim

Department of Sericulture and Entomology, The National Institute of Agricultural Science & Technology, Rural Development Administration, Suwon 441-100, Korea.

(Received 27 April 2002; Accepted 2 June 2002)

Cocoon production, which is a representative of traditional sericulture shifted into silkworm powder production in the spring of 1995. This, infect, signifies the change from the dress-centered textile business to the bio-industry and the functional resource industry. One of the most outstanding shifting is utilization of silkworm larvae for anti-diabetic agent. In Asian countries including Korea, silkworm powder derived from the domestic silkworm (*Bombyx mori* L.) has long been favored for anti-diabetic agent, but its efficacy was not tested until last decade by modern scientific methods. In this article, we reviewed the major researches on the silkworm powder as a blood glucose-lowering substance. After the beginning test of the efficacy of silkworm powder by a cooperative research between Department of Sericulture and Entomology, NIAST, RDA and Kyung Hee University, substantial data have been accumulated so far. In a serial experiment to select best condition, the fifth instar larvae prepared by freeze dry method turned out to have the best blood glucose-lowering effect. In the pharmacological experiment to understand the mechanism of silkworm powder in small intestine, the silkworm powder turned out to inhibit the activity of α-glucosidase, by competitively binding to α-type disaccharides. The animal experiment showed that the extract of silkworm powder prevents a rapid increase of blood glucose level after meal and prevents hunger and low blood glucose level during empty stomach. In the experiment to isolate the major component of silkworm powder, which exerts blood glucose-lowering effect, 1-deoxynojirimycin (DNJ) was eventually mass-purified, and it turned out that DNJ isolated from silkworm powder was excellent in its blood glucose-lowering effect. In the experiment to understand the personal difference of the efficacy of the silkworm powder, clinical candidates were divided on the basis of the criterion of traditional Chinese medicine: Tae-Yang, Tae-Um, So-Yang, and So-Um. The result showed that silkworm powder has a tendency to reduce blood glucose level at fasting and at 2 hours after meal, and this trend was somewhat obvious in the Tae-Um body type. In summary, we reviewed scientific papers on the efficacy of silkworm powder and its purified DNJ as a blood glucose-lowering agent. These suggest that silkworm powder truly possesses blood glucose-lowering effect as documented in the traditional Chinese medicine, although further researches will be required to develop them as "medical" resource instead of functional food.

Key word : Silkworm, *Bombyx mori*, Silkworm powder, Diabetes, Blood glucose, Sasangurhak, 1-deoxynojirimycin, DNJ

*To whom correspondence should be addressed.
Department of Sericulture and Entomology, The National Institute of Agricultural Science & Technology, Rural Development Administration, Suwon 441-100, Korea.
Tel: +82-31-290-8470; Fax: +82-31-295-2176;
E-mail: ksryu@rda.go.kr

Introduction

The traditional sericulture sifted from the cocoon production to functional sericulture, in which the dress-centered textile business was moved into the advanced bio-industry emphasizing a diverse utility of sericultural products. One of such a big movement to new application of sericultural products is utilization of silkworm itself from the source of cocoon production to food stuff, medical source, biotech application and so on (Lee and Kim, 2000; Kim, 1999).

Traditionally, sericultural by-products have been favored for the raw materials of Chinese medicine, especially for anti-diabetic agent in Korean and China, but scientific examination of the efficacy has to be tested. Asano *et al.* (1994) isolated N-containing sugars from the root of mulberry tree, *Morus alba*, and reported that mulberry root truly exert glycosidase inhibitory activities, which is a necessary mechanism for the control of blood glucose level. However, other sericultural products did not get much attention as blood glucose-lowering agent until recently. This is partially because the major component controlling blood glucose-level was believed to be included in the mulberry leaves. Nevertheless, many peoples in Korea have long been utilized silkworm powder traditionally to control diabetes without doubt, because the staple food for silkworm larvae is mulberry leaves. From 1995 scientific reexamination of silkworm powder was initiated and substantial information is accumulated until now. In this report, we reviewed the recent study trend of silkworm powder to better understand the significance and the mechanisms of silkworm powder as a blood glucose-lowering agent.

Silkworm powder for anti-diabetes

Difference in the blood glucose-lowering level by manufacturing process

It has been recorded that a few sericultural by-products such as silkworm feces, mulberry leaves, and silkworm pupae have been known to exert an anti-diabetic effect traditionally (Asano *et al.*, 1994a; Lee *et al.*, 1998; Kim *et al.*, 1999). Among these, silkworms showed better efficacy for the decrease of blood glucose level by the cooperative study between Department of Sericulture and Entomology, The National Institute of Agricultural Science & Technology (NIAST), Rural Development Administration (RDA) and Kyung Hee University (Ryu *et al.*, 1997).

Silkworm is holometaboly insect: it undergoes egg stage, five larval stages, pupal stage and moth stage. During and at each stage, silkworms undergo changes in the physiology and levels of biologically active substances. Therefore, it is critical to select a proper stage to maximize the efficacy of silkworm powder as a blood glucose-control agent. Also, selection of proper preparation method is important, because the efficacy varies depending on the manufacturing method. In a traditional fork remedy, the heat-dried silkworms prepared at the 5th instar larvae were favored. However, this "heat method" may inactivate various enzymes presented in the silkworms. Another problem of the "heat method" is oxidation of

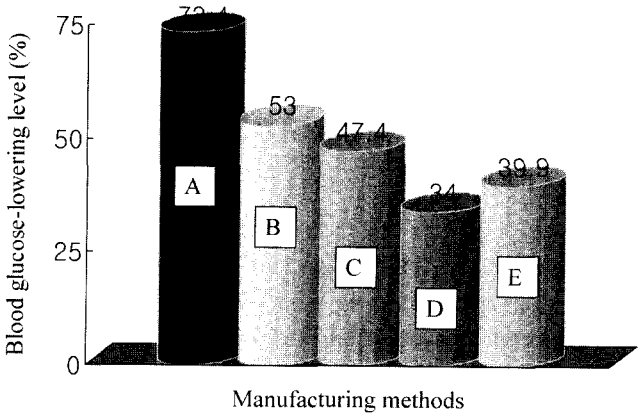

Fig. 1. Effect of silkworm powder prepared by several different manufacturing methods (Ryu *et al.*, 1997). A, silkworm powder prepared from freezed-dried silkworm; B, heat-dried silkworm; C, fasting silkworm; D, artificial diet silkworm; and E, molting silkworm.

silkworm powder. A large portion of the inside of silkworm body is occupied by midgut, filled with mulberry leaf particles, feces, hemolymph, and several enzymes secreted by silkworms. Because the digesting enzymes and hemolymph in the midgut possess a strong oxidative capability, they are easily oxidized and inactivated. Thus, the traditional on-the-market silkworm powder mostly sheds a black color. To overcome these problems, which weaken the pharmacological efficacy of silkworm powder, several attempts have been made to select best method, and the result is as follows (Fig. 1).

Freeze-dried silkworm powder

According to Chung *et al.* (1996), the best stage for silkworm larvae as a blood glucose-lowering agent is 5th instar larvae. With the silkworm powder prepared at this stage, animal experiment for efficacy test was carried out. Mice were fed the silkworm powder prepared by freeze-drying method or heat-drying method, and the freeze-dried silkworm group showed the best result in lowering blood glucose level (73.4% reduction compared with control group; Chung *et al.*, 1996; Ryu *et al.*, 1997). This value is notable in that the heat-dried silkworm group only reduced to 53% of original blood glucose level. It appears that the lower efficacy in the "heat method" may have stemmed because various enzymes contained in the silkworm body are inactivated and oxidation is accelerated by heat.

Silkworm powder prepared from abstained silkworm

Because sericultural farmers suffer from a shortage of hands, sometimes they leave the third day of fifth instar larvae unattended for a while after providing seventh feed

during fifth instar, which is the last feed to reach to the stage of the third day of fifth instar larvae. Furthermore, this fasting hours tend to continue until subsequent morning, although the best time as a blood glucose-lowering agent is recommended to be 1 - 2 hrs after the seventh feed. In order to demonstrate the effect of fast, mice were fed the silkworm powder prepared with 24-hour-fasting silkworms, and blood glucose level of the mice was measured. The fasting silkworm powder group was lower in the blood glucose reduction than its control, the freeze-dried silkworm group. The research demonstrates that silkworm larvae should eat enough mulberry leaves to fill their intestine with mulberry-leaf particles. When farmers are suffered from busy schedule, they should though at least provide least amount of mulberry leaves necessary for the silkworms to fill up their intestine. Another way to minimize low efficacy of silkworm powder as blood glucose-lowering agent is to start bruishing of silkworm larvae with less amount than usual or start with a few days of interval. Nevertheless, the best way to sustain the pharmacological efficacy of silkworm powder is to process them without delay after the last feed during fifth instar.

Silkworm powder prepared from artificial diet silkworm

To overcome the shortage of hands, silkworm rearing with artificial diet has long been encouraged, especially during 5th instar. Thus, many farmers have asked whether there is any difference present in the blood glucose-lowering effect between the silkworm powder prepared by artificial-diet-silkworms and natural-diet-silkworms. The experiment to find out the difference showed low efficacy in the artificial diet group than fasting silkworm group (47.4% vs. 34%). This result is reasonable in that artificial diet contains only 20% of mulberry-leaf powder compared with natural mulberry leaves. This low level of efficacy has been suggested to be insufficient for the decrease of blood glucose level.

Silkworm powder prepared from molting silkworm

Silkworms undergo four times of molting to grow during their larval stages. The respective step of molting is seemingly very serious and, in fact, tremendous hormonal changes are accompanied inside silkworm body. For this reason, many scientists have investigated the physiological changes and processes during ecdysis (Patton, 1963). Thus, sericultural farmers and the general run of people have vaguely believed that the silkworm larvae in the middle of molting might have better blood glucose-lowering effect. However, Ryu *et al.* (1997) found a reverse result: the least blood glucose-lowering effect was found in the mice group fed silkworm powder prepared using molting silkworm (39.9% compared with other methods; Fig. 1), and, thus, such silkworm larvae are not recommendable for silkworm powder.

In summary, the blood glucose-lowering effect has been tested with several preparation methods. Because the possible major component controlling blood glucose level in the silkworm powder is derived from mulberry leaves, it is very critical to keep the mulberry parcels inside silkworm body. To help this, the 5th instar larvae should be processed without delay. When long-distance transfer is required, enough mulberry leaves should be provided for the silkworms not to hungry. And also, the better result obtained from the freeze-drying method compared with heat-drying method suggests that minimum denatureation of the silkworm component during drying process is an important factor for the efficacy. In addition, later than the third day at 5th instar may deteriorate the quality of powder per unit, because silkworm develop its silk, and it occupies about 40% of silkworm weight until seventh ~ eighth days of 5th instar larvae.

Pharmacological mechanisms of silkworm powder

Pharmacological mechanisms of silkworm powder

The bulk of the organic materials in food consists of proteins, fats, and carbohydrates in the form of starch and other polysaccharides. Although these are suitable raw materials, humans cannot use them directly, partially because these molecules are too large to pass through membranes and enter the cells of humans. Thus, digestion cleaves macromolecules into monomers. For instance, polysaccharides and disaccharides are split into simple sugars.

Although there is no nutritional requirement for carbohydrate, it is usually the principal source of calories for most humans. The plant starch amylopectin is the major source of carbohydrates in the diet of most humans, which is a large (10^6 MW and larger) branched polymer of glucose monomers. Once humans eat foods and chew them, salivary α-amylase cleaves interior α-1,4 linkages in starch. Salivary amylase can break only every other bond in the polysaccharides, so the smallest product of this digestion is maltose, maltotriose, longer α-1,4 linked linear glucose polymers, and α-limit dextrins. Amylase action continues until food is acidified in the stomach, but it does not complete digestion of starch. Once salivary amylase is inactivated, no further digestion of starch occurs in stomach. Pancreatic juice has a high activity of α-amylase. Specificity and products are same as salivary amylase. Within 10 min of entering the duodenum, starch is almost com-

pletely converted to the oligosaccharide products.

Although limited digestion of starch takes place in the oral cavity and partial digestion of proteins by pepsin occurs in the stomach, most enzymatic hydrolysis of the macromolecules in food occurs in the small intestine. With a length of more than 6 m, the small intestine is the longest section of the alimentary canal. Lactase splits lactose into glucose and galactose. Sucrase splits sucrose into glucose and fructose. Glucoamylase cleaves terminal α-1,4 linkages. Isomaltase debranches α-limit dextrins by cleaving α-1,6 linkages at the branch points. In digesting an α-limit dextrin, this group of enzymes tends to remove one glucose unit at a time from the non-reducing end of the molecule (Legler, 1990; Baron, 1998). Furthermore, the small intestine is responsible for the absorption of most nutrients into the blood.

Silkworm powder follows normal pathway of food digestion and reaches to the small intestine. Once silkworm powder reaches to the small intestine, it inhibits the activity of one of the oligosaccharidases, α-glucosidase, by combining to the enzyme competing with α-type disaccharides such as mannose, sucrose and so on. Therefore, this binding prevent sudden hydrolysis of disaccharides, absorption of glucose into the blood vessel, and resultant increase of blood glucose level (Fig. 2; Bressler and Johnson, 1992).

Recently, the oral α-glucosidase inhibitor, Acarbose, has been prescribed to the Type-II diabetic patients, and clinical experiments are actively performed. This drug has a merit because it does not cause hypoglycemia, although it does delay digestion and absorption of complex carbohydrates and lessens high blood sugar level right after meals and hyperinsulinism (Balfour and McTavish, 1993; Salvatore and Giugliano, 1996; Clissold and Edwards, 1998; Scott and Spencer, 2000). Furthermore, this drug is known to mitigate levels of blood glucose, neutral fats, and cholesterol. On the other hand, the drug is known to cause borborygmus, diarrhea, and abdominal inflation (Ramaswamy and Flint, 1980). The patients who took silkworm powder occasionally also claimed to have the same side effect such as borborygmus and abdominal inflation.

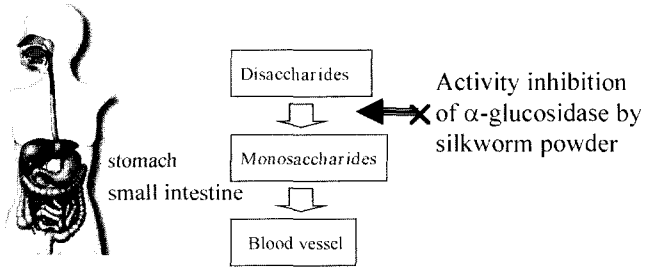

Fig. 2. Pharmacological mechanism of silkworm powder.

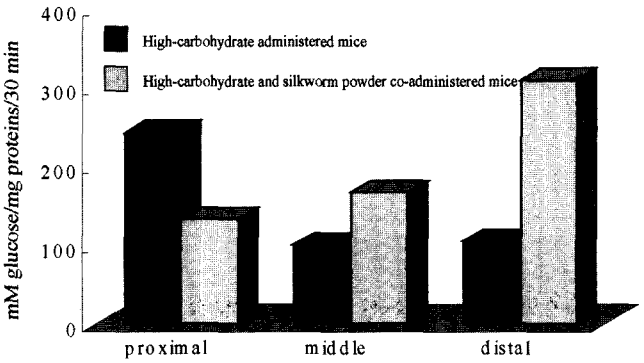

Fig. 3. Maltase activities in three portions of small intestine of the mice administered to high carbohydrate alone and co-administered to high carbohydrate and silkworm extract.

Activation of glucosidase after administration of silkworm powder

In the experiment to investigate the absorption profile of blood glucose in the mice administered to MeOH extract derived from silkworm powder, it turned out that silkworm powder inhibits the transient rising of blood glucose level after postprandial 30 min through inhibition of α-glucosidases (Ryu *et al.*, 1999). This result may suggest that silkworm powder can be eaten during food ingestion. In the experiment to investigate the effect of the extract from silkworm powder on the blood glucose level and intestinal glucosidase activity, the mice administered to high carbohydrate concentration showed a trend of disappearance of hyperglycemia and hyperinsulinemia (Chung *et al.*, 1997). Also, silkworm extract co-administered with high carbohydrate diet to mice for ten weeks significantly induced maltase, sucrase and lactase activities. This activation was significant particularly in the middle and obviously in the distal portion of small intestines of the mice (Chung *et al.*, 1997). In another word, inhibition of glucosidases was weakened as carbohydrates pass through the small intestine. This, in turn, means that silkworm powder controls a rapid increase after meal and, at the same time, prevent hunger and low blood glucose level during empty stomach.

Mass-purification of blood glucose-lowering substance and its efficacy

Mass-purification of blood-glucose lowering substance

Although silkworm has been widely favored as blood glucose-lowering agent by many Koreans, one of the frequent questions asked on the silkworm powder was its major component exerting blood glucose-lowering effect. In a cooperative research between Department of Sericulture

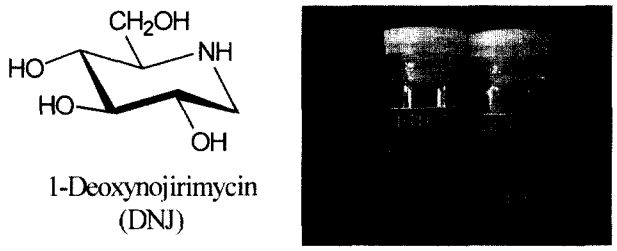

Fig. 4. Chemical structure of isolated 1-deoxynojirimycin (left panel) and its crystallized pure form in the bottle (right panel).

and Entomology, NIAST, RDA and Seoul Sam-Sung Medical Center in 2000, the major component of silkworm powder, named 1-deoxynojirimycin (DNJ) was finally isolated (Fig. 4; Kim *et al.*, 2000). DNJ is an alkaloid belonging to polyhydroxylated piperidine and has been reported to be contained abundantly in the mulberry leaves and its root (Asano *et al.*, 1994a,b; Asano *et al.*, 1995; Asano, 2000; Asano *et al.*, 2001). Furthermore, this substance has been known to be one of the major blood glucose-lowering substances among a diverse mulberry extract and a powerful competitive inhibitor for α-glucosidase (Asano *et al.*, 1995; Chen *et al.*, 1995; Kimura *et al.*, 1995; Lee *et al.*, 1998). Thus, the chemical itself is not a new one.

The structure of DNJ from silkworm powder was determined by a variety of 1D and 2D NMR spectral data and HRFABMS, and the yield was 0.3%. Asano *et al.* (1994b) have previously reported an isolation of DNJ from the root bark of *Morus* sp., and the yield was 0.11%. Also, Yagi (1987) has reported the isolation of 1-deoxynojirimycin with the yield of 0.14% from the roots of *Morus* sp. However, it is surprising in that silkworm accumulates such a high concentration per silkworm weight enough to exert an obvious blood glucose-lowering effect.

Efficacy of DNJ

The blood glucose-lowering effect of DNJ isolated from silkworm powder was tested with a cooperative research between Department of Sericulture and Entomology, NIAST, RDA and Seoul Sam-Sung Medical Center (Kim *et al.*, 2000). Male rats of SD-strain (200 g) were injected with 65 mg/kg of STZ (Sigma, St Louis, MO, USA) dissolved in 0.1 M citrate buffer in the abdominal cavity. Blood glucose levels of these rats were higher than 350 mg/dL before each experiment. The 20 mg/kg concentration of DNJ were dissolved and were oral-injected into the STZ rat for 10 days and blood glucose level was checked for 14 days. Acarbose utilized as control was suspended in the saline and was also oral-injected at the 20 mg/kg.

From the experiment, it was shown that blood glucose

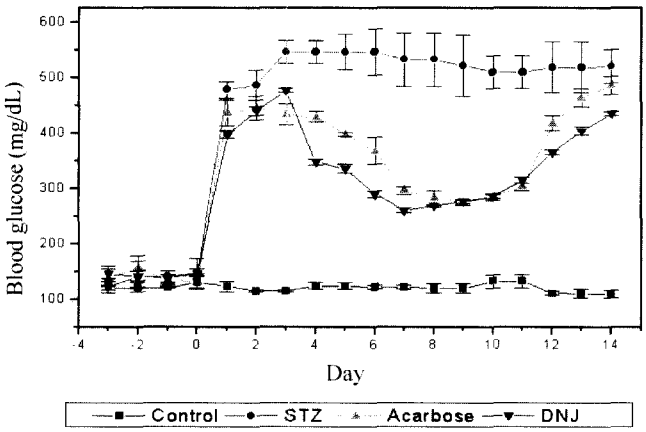

Fig. 5. Effect of DNJ and Acarbose injection on the blood glucose level of mice.

level was sustained more than 450 mg/dL in the hyperglycemic group induced by streptozotocin during the experimental period (Fig. 5). The reduction level of blood glucose was 47.1% in the mice injected with 20 mg/kg of DNJ for 4 days and the result was statistically significant. Thus, DNJ isolated from silkworm powder was excellent in its blood glucose-lowering effect. Furthermore, this low blood glucose level was maintained to the degree of 50% from 4 to 11 days during experimental period. These results suggest that the DNJ derived from silkworm powder can be utilized for NIDDM (Non-Insulin Dependent Diabetes Millitus) patients. On the other hand, the control group injected with Acarbose showed the effect of drug from 7th days with the reduction rate of 57.6%. Thus, DNJ was somewhat better than Acarbose in its onset of effect. When mice were stopped for the injection of DNJ and Acarbose, respectively, blood glucose level increased sharply in both groups. Thus, DNJ derived from silkworm powder seems to have almost an identical mechanism for blood glucose control.

Clinical experiment with powdery silkworm

Although silkworm powder has been used to treat diabetes mellitus traditionally and the consumption increased tremendously, the effect was said to differ by person to person. Probably, many factors are involved, but it may not easy to find out the exact source of difference. Nevertheless, it seems to be important to try to find out the source of difference to better cure diabetes. In one experiment to find the source of difference, diabetic patients were subdivided into four types, based on their characteristics of body. This design is plausible in that traditionally peoples in Asian countries such as Korea and China were divided

into four groups based on their body types. Different body type has a difference in physiology and pathology of the disease, disease susceptibility, and disease development. This kind of oriental medicine is called Sa-Sang-Ur-Hak. The four body types are Tae-Yang, Tae-Um, So-Yang, and So-Um. Tae-Yang person has more energy from sun light, and Tae-Um has more energy from moon shade, and So-Yang has small energy from sun light, and So-Um has small energy from moon shade. For the experiment, each type of persons with diabetes was subdivided into two groups: ones taking diabetic drug together with silkworm powder and the others taking silkworm powder alone (Ryu *et al.*, 2000). The Tae-Yang group was not included because it mostly does not apply to Asian people and enough number of diabetic patients was not applied to this category. Thus, only three groups were subjected to the experiment. Blood glucose levels ranged from 138.1~153.5 mg/dL in the three body-type groups, regardless of drug application (Table 1). However, it was higher in the drug application group, although there was no statistical difference between them.

Blood glucose level at fasting

In the drug group (provided both regular diabetes drug and silkworm powder), there was a significant difference in the blood glucose level among body types, when measured at the time before meal. For example, at 2 weeks, the highest reduction was detected in the Tae-Um (13.4%), next in the So-Yang (10.5%) and least in the So-Um (5.2%) compared with its own control, and these differences were statistically significant ($p < 0.05$). At 4 weeks, the highest reduction was detected in the Tae-Um (15.5%), next in the So-Yang (15.0%) and least in the So-Um (8.3%), and statistical significance was observed only in a comparison between Tae-Um and So-Um ($p < 0.05$). In the non-drug group (provided silkworm powder only), there was no significant difference in the blood glucose level among body types, although the reduction degree was high in the order of Tae-Um (8.3%), So-Yang (5.7%) and So-Um (4.7%) at 2 weeks. On the other hand, at the highest reduction was shown in So-Yang (12.5%), next Tae-Um (11.8%) and least in the So-Um (7.2%), but no statistical significance in the difference was obtained at 4 weeks. Furthermore, no other statistical significance was obtained in the comparison of among-body types and between drug and non-drug applications.

Blood glucose level at 2 hours after meal

Blood-glucose level measured at 2 hours after meal ranged from 250.7~273.0 mg/dL. There was no statistical significance in the difference among body types whether they take diabetes drug and silkworm powder (drug group) together or silkworm powder alone (non-drug group), but non-drug group was higher than drug-taking group in the blood glucose level (Table 1).

In the comparison of the 2nd week blood glucose level at 2 hours after meal, the reduction rate was high in the order of Tae-Um (15.7%), So-Yang (11.8%) and So-Um (10.8 %) in the drug group, but the values were not statistically different. In the comparison of the 4th week blood glucose level at 2 hours after meal, the reduction rate was in the order of Tae-Um (24.8%), So-Yang (19.4%) and So-Um (14.6%) in the drug group. Although there was no statistical difference between Tae-Um and So-Yang, it was

Table 1. Changes of blood glucose level at fasting and two hours after meal (*unit*: mg/dL)

		0 week	2 weeks	4 weeks	8 weeks
At fasting					
Tae-Um	Drug	142.4±32.5	123.3±35.4(13.4)	120.3±36.8(15.5)	133.7±31.6(93.9)
	Non-drug	153.5±42.7	140.73±3.8(8.3)	135.4±38.2(11.8)	144.8±36.1(94.3)
So-Yang	Drug	147.9±32.6	132.3±32.7(10.5)	125.7±34.3(15.0)	135.9±35.3(91.9)
	Non-drug	150.1±40.2	141.5±35.2(5.7)	131.3±38.6(12.5)	142.6±36.5(95.0)
So-Um	Drug	138.1±30.7	130.9±32.5(5.2)	126.7±33.4(8.3)	133.3±35.4(96.5)
	Non-drug	145.2±32.5	138.4±30.6(4.7)	134.8±33.5(7.2)	139.2±35.0(95.9)
2-hours after meal					
Tae-Um	Drug	256.1±58.4	215.8±72.6(15.7)	192.7±62.6(24.8)	223.4±58.4(87.2)
	Non-drug	268.0±68.2	236.5±57.3(11.8)	212.1±72.6(20.9)	246.5±63.1(92.0)
So-Yang	Drug	261.1±62.8	230.8±58.6(11.6)	210.4±63.0(19.4)	233.6±62.2(89.5)
	Non-drug	273.0±67.4	245.3±62.7(10.2)	230.1±60.9(15.7)	246.5±63.8(90.3)
So-Um	Drug	250.7±66.1	223.6±64.5(10.8)	214.1±65.8(14.6)	227.1±58.4(90.6)
	Non-drug	264.3±65.2	237.1±62.9(10.3)	223.6±66.1(15.4)	240.9±60.6(91.1)

significant between Tae-Um and So-Um ($p < 0.05$). Thus, the drug-group result partly supports the presence of difference in the silkworm powder susceptibility on the basis of traditionally defined body types.

In the comparison of the 2nd week blood glucose level at 2 hours after meal, the reduction rate was high in the order of Tae-Um (11.8%), So-Yang (10.2%) and So-Um (10.3 %) in the non-drug group, but the values were not statistically different. In the comparison of the 4th week blood glucose level at 2 hours after meal, the reduction rate was in the order of So-Yang (19.4%), Tae-Um (15.7%), and So-Um (15.4%) in the non-drug group. After accomplishment of silkworm powder taking, all groups showed recovery of the blood glucose level to 90% of original state (0 week), and the degree of recovery was not different on the basis of body types, and also whether or not they take drug. Conclusively, it has been demonstrated that silkworm powder has a tendency to decrease blood glucose level at fasting and at 2 hours after meal, especially for Tae-Um body type. Although Tae-Um body type showed better decrease ratio that other body types, Ryu *et al.* (2000) suggested that a well designed experiment which minimizes disturbing parameters such as other disease, sex, age, diet habit and so on could better define susceptibility of silkworm powder as a blood glucose-lowering agent.

The data were compared with the result of clinical experiment of Migritol, which is a commercialized, registered, orally administering drug for Type 2 diabetes mellitus. An equivalent comparison is not possible yet, because the drug has already been commercialized and passed through all necessary tests for registration (Scott and Spencer, 2000). However, silkworm powder is comparable with Migritol in that the major component of Migritol is a DNJ-derivative. In the blood glucose level at fasting, Migritol showed 6.8%~12.5% reduction and silkworm powder was 7.2%~15.5% after taking for 4 weeks (data not shown). Also, blood glucose level at 2 hours after meal showed 7.3%~21.2% reduction in Migritol and silkworm powder was 15.4%~24.8%. Just on the basis of the data compared here, it appears that silkworm powder is at least equivalent to the commercialized Migritol. However, the given data still provide the ground for subsequent extended clinical experiment to develop silkworm powder as a specialized drug for Type II diabetes mellitus. Although the experiment of Sa-Sang-Ur-Hak is not a perfect design yet, the experiment will be useful background and start point to test the personal difference of the drug susceptibility. In fact, after human genome project (HGP) is completed, Western scientists are actively collect genome data from different races, family, and even to the persons to figure out the genetic difference of the drug susceptibility and to develop "designed drug" suitable for each persons genetic need. In this regard, the traditional Asian Sa-Sang-Ur-Hak may be another version of "designed medicine".

References

Asano, N. (2000) Alkaloidal sugar mimics: biological activities and therapeutic applications. *J. Enz. Inhibition* **5**, 215-234.

Asano, N., K. Oseki, E. Tomioka, H. Kizy and K. Matsui (1994a) N-containing sugar from the *Morus alba* and their glycosidase inhibitory activities. *Carbohd. Resc.* **259**, 243-255.

Asano, N., E. Tomioka, H. Kizu, and K. Matsui (1994b) Sugars with nitrogen in the ring isolated from the leaves of *Morus bombysis*. *Carbohydr. Res.* **253**, 235-245.

Asano, N., H. Kizu, K. Oseki, E. Tomioka, and K. Matsui (1995) *N*-alkylated nitrogen-in-the ring sugars: conformational basis of inhibition of glycosidases and HIV-replication. *J. Med. Chem.* **38**, 2349-2356.

Asano, N., T. Yamashita, K. Yasuda, K. Ikeda, H. Kizu, Y. Kameda, A. Kato, R. J. Nash, H. S. Lee and K. S. Ryu (2001) Polyhydroxylated alkaloids from mulberry trees (*Morus alba* L.) and silkworms (*Bombyx mori* L.). *J. Agric. Food Chem.* **49**, 4028-4213.

Balfour, J. A. and D. McTavish (1993) Acarbose: an update of its pharmacology and therapeutic use in diabetes mellitus. *Drugs* **46**, 1025-1054.

Baron, A. D. (1998) Postprandial hyperglycaemia and α-glucosidase inhibitors. *Diabetes Res., Clin. Pract. Suppl.* **40**, 51-55.

Bressler, R. and D. Johnson (1992) New pharmacological approaches to therapy of NIDDM. *Diabetes Care* **15**, 797-805.

Chen, F. J., N. Nakashima, I. Kimura, and M. Kimura (1995) Hypoglycemic activity and mechanism of extracts from mulberry leaves and cortex mori radices in streptozotocin induced diabetic mice. *Yakugaku Zasshi* **115**, 476-482.

Chung, S. H., M. S. Kim and K. S. Ryu (1997) Effect of silkworm extract on intestinal α-glucosidase activity in mice administered with a high carbohydrate-containing diet. *Korean J. Seric. Sci.* **39**, 86-92.

Chung, S. H., J. H. Yu, E. J. Kim and K. S. Ryu (1996) Blood glucose lowering effect of silkworm. *Bull. K. H. Pharma. Sci.* **24**, 95-100.

Clissold, S. P. and C. Edwards (1998) Acarbose: a preliminary review of its pharmacodynamic and pharmacokinetic properties, and their apeutic potential. *Drugs* **35**, 214-243.

Kim, K. W., S. W. Seo, K. S. Ryu, H. S. Lee, J. W. Kim, I. Kim, Y. K. Lee, M. Y. Ahn and E. S. Kim (2000) A process for preparing α-glucosidase inhibitor derived from powdery silkworm. Patent. Registration number submission number 2001-0011449.

Kim, S. Y. (1999) Illustration of functionality in the mulberry leaves; in *Prospect for the utilization of the bio-active substances in the mulberry leaves as food.* Lim, S. H. (ed.), pp.19-42, The Korean Society of Sericultural Science, Seoul, Korea.

Kim, S. Y., K. S. Ryu, W. C. Lee, H. O. Ku, H. S. Lee and K. R. Lee (1999) Hypoglycemic effect of mulberry leaves with anaerobic treatment in alloxan-induced diabetic mice. *Kor. J. Pharmacogn* **30**, 123-129.

Kimura, M., F. Chen, N. Nakashima, I. Kimura, N. Asano, and S. Koya (1995) Antihyperglycemic effects of *N*-containing sugars derived from mulberry leaves in streptozocin diabetic mice. *J. Trad. Med.* **12**, 214-219.

Lee, H. S., K. S. Chung, S. Y. Kim, K. S. Ryu and W. C. Lee (1998) Effect of several sericultural products on blood glucose lowering for alloxan-induced hyperglycemic mice. *Korean J. Seric. Sci.* **40**, 38-42.

Lee, W. C. and I. Kim (2000) The strategy for the development of bio-resources utilizing sericultural products and insects. *Int. J. Indust. Entomol.* **1**, 95-102.

Legler, G. (1990) Glycoside hydrolases: mechanistic information from studies with reversible and irreversible inhibitor. *Adv. Carbohyd. Chem. B* **48**, 319-385.

Patton, R. L. (1963) Introductory insect physiology. W. B. Saunders Company, Philadelphia and London.

Ramaswamy, K. and P. W. Flint (1980) Effect of genetic diabetes on enzyme of mouse intestinal brush-border membrane. *Am. J. Physiol.* **286**, 6114.

Ryu, J. H., N. J. Kim, J. C. Oh, J. H. Chun and B. J. Lee (2000) Effect of silkworm powder on four Asian body types; in *A clinical experiment of the blood-glucose lowering substances, powdery silkworm, by Western and Chinese medicine*. Ryu, K. S. (ed.), pp. 77-97, Korean Sericulture Association, Seoul, Korea.

Ryu, K. S., H. S. Lee, S. H. Chung and P. D. Kang (1997) An activity of lowering blood-glucose levels according to preparative conditions of silkworm powder. *Korean J. Seric. Sci.* **39**, 79-85.

Ryu, K. S., H. S. Lee and S. Y. Kim (1999) Pharmacodynamic study of silkworm powder in mice administered to maltose, sucrose and lactose. *Korean J. Sric. Sci.* **41**, 9-13.

Salvatore, T. and D. Giugliano (1996) Pharmacokinetic-pharmacodynamic relationships of acarbose. *Clin. Pharmacokinet.* **30**, 94-106.

Scott, L. J. and C. M. Spencer (2000) Miglitol: a review of its therapeutic potential in type-2 diabetes mellitus. *Drugs* **59**, 521-549.

Yagi, K. (1987) Lipid peroxides and human diseases. *Chem. Physics Lipids* **45**, 337-351.