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Anti-Diabetic Activity of Maitake Mushroom Extract (SXF) on Diabetic KK-A^y Mouse

Sensuke Konno[1*], Daniel Bassily[1], Charles White[1], Sean Fullerton[1], Cun Zhuang[2]

[1]Department of Urology, New York Medical College, Valhalla, NY, USA
[2]Mushroom Wisdom Inc., East Rutherford, NJ, USA
Email: *sensuke_konno@nymc.edu

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Abstract

A lack of specific and effective treatment for Type 2 diabetes has long demanded to establish a better therapeutic modality. As the maitake mushroom extract, SX-fraction (SXF), has been shown to have anti-diabetic activity, we investigated if SXF would demonstrate such an activity in diabetic KK-A^y mice. Test materials included original maitake mushroom (Orig-M), two different doses of SXF [low dose of SXF (L) and high dose of SXF (H)], and Actos® (ACT). Two hundred KK-A^y mice were divided into five experimental groups: (A) Sham (none given), (B) Orig-M, (C) SXF (L), (D) SXF (H), and (E) ACT. Mice received these materials for 8 weeks, while the experimental conditions, such as body weight and diabetic/lipid parameters, were monitored every two weeks. No significant changes in body weight were seen in all experimental groups. Regarding diabetic parameters, the serum glucose (GLC) levels in the groups B and C were significantly lower than the Sham group (A) at 2 weeks. The GLC decline was seen further in the groups C and D at 8 weeks. However, the levels of 1,5-anhydro-D-glucitol (1,5-AG), a marker used for the short-term glycemic control, showed no significant changes between the groups. The significant reduction in the serum insulin (INS) levels was yet detected in the group D at 8 weeks. Serum lipid parameters, *i.e.*, serum triglyceride (TGL), total cholesterol (CHL), and high-density lipoprotein (HDL), in the groups (B-E) were noticeably higher than the Sham (A) group, although such differences were not statistically significant. In conclusion, SXF appears to significantly lower the GLC and INS levels in KK-A^y mice. However, no significant changes or improvements in lipid parameters (TGL, CHL, and HDL) were found with SXF. Nonetheless, this study demonstrates that SXF has anti-diabetic activity, capable of improving certain diabetic conditions.

Keywords

SX-Fraction, Diabetes, Anti-Diabetic Activity, Diabetic Parameters, Lipid Parameters

1. Introduction

Diabetes mellitus, or simply *diabetes* is the metabolic disorder with a chronic high blood glucose level [1]. This could yet provoke serious clinical complications, such as retinopathy, neuropathy, and nephropathy, subsequently leading to blindness, renal failure, amputation, coma, and death [2] [3]. Nearly 50 million US population might have diabetes (including undiagnosed) in 2025 and its incidence keeps rising every year [4]. Hence, it is urgently needed to control or stop steadily growing such an incidence.

Diabetes is classified into two types: Type 1 (insulin-dependent diabetes) and Type 2 (non-insulin-dependent diabetes) [5]. Type 1 diabetes is primarily caused by insulin deficiency, representing <10% of all cases of diabetes, while Type 2 diabetes with a >90% incidence rate [6] involves multiple factors, such as defects in insulin secretion, insulin resistance (at muscle and adipose tissue), and elevated hepatic glucose production [7] [8]. Regarding treatment, Type 1 diabetes, due directly to insulin deficiency, is relatively more manageable through insulin injection; however, Type 2 diabetes is not primarily linked to insulin deficiency but rather linked to *peripheral insulin resistance*, *i.e.* insulin insensitivity at peripheral sites [8]. Due to this insulin resistance, current oral therapy using sulfonylurea derivatives [7], stimulating insulin secretion from pancreas, was often unsatisfactory. Medications such as troglitazone and metformin were also developed to enhance peripheral insulin sensitivity [9] [10]. Despite some improvements in glycemic control, they have been reported to have potential adverse effects. Because of these drawbacks, it makes even harder to adequately and effectively treat Type 2 diabetes. Hence, more effective treatment must rely mainly on *how to* overcome insulin resistance, but it should be also *safer* unlike drugs currently being used.

We were particularly interested in a *natural* extract called, SX-fraction (SXF), obtained from maitake mushroom (*Grifola frondosa*). SXF is a water-soluble glycoprotein with a molecular weight of ~20,000 Da, and a number of scientific/medical studies have been performed, including its hypoglycemic and anti-diabetic activity on diabetic mice [11]-[13]. Hence, the safety of SXF is acceptable based on these animal studies and it unlikely has side effects because of its natural nature. Now, it is worth mentioning that maitake mushroom is not just another mushroom but has promising potentials. While it is an edible, tasty mushroom often used in cooking, it has provided us with certain health benefits as well. Prior to SXF, another distinct extract called, Maitake D-fraction (PDF), was initially extracted from this mushroom. A number of studies conducted on PDF in the past 40 years then revealed its significant medicinal and physiological properties, in-

cluding anticancer, immunostimulatory, anti-viral activities etc. [14]-[16]. In addition, the safety of PDF was also granted by the facts that the US Food and Drug Administration (FDA) exempted it from a Phase I Toxicology study and approved it for the Investigational New Drug (IND) application as well [17]. Thus, this further confirms the safety of maitake mushroom extracts (PDF and SXF), which can be taken safely by patients as well as normal subjects.

Accordingly, we investigated if original maitake mushroom or a different dose of SXF given would indeed have anti-diabetic activity on diabetic KK-A^y mice, which are widely used as an excellent model for the studies related to Type 2 diabetes [18]. Several diabetic and lipid parameters, such as the levels of serum glucose (GLC), insulin (INS), triglycerides (TGL), total cholesterol (CHL), and high-density lipoprotein (HDL), were recorded for 8 weeks. Any positive or negative effects on these parameters were rationally interpreted and discussed herein.

2. Methods

2.1. Animals

A total of 200 female KK-A^y mice (4 weeks old) were purchased from The Jackson Laboratory (Bar Harbor, ME). They were employed in this study because they spontaneously exhibit hyperglycemia, hyperinsulinemia, and insulin resistance [18] [19], whose conditions are similarly found in Type 2 diabetic patients. All mice were acclimatized for eight days in a room of the animal facility with controlled temperature (23˚C ± 2˚C), humidity (55% ± 15%), ventilation (15 changes/h), and light (12-h light/dark cycles). They were also provided with standard chow and free access to water.

All experimental materials and procedures were approved (#10-2-0216) by the Institutional Animal Care and Use Committee (IACUC) at New York Medical College (Valhalla, NY). Experimental conditions are described in **Table 1** below.

Table 1. Experimental conditions.

Materials Given	Experimental Groups	Dosage Used
Control (None given)	Sham	None
Original Maitake Powder	Orig-M	5.0 g/kg weight
Low Dose of SXF	SXF (L)	0.5 g/kg
High Dose of SXF	SXF (H)	1.5 g/kg
Pioglitazone HCl (Actos®)	ACT	30 mg/kg

All experimental materials were mixed with regular chow and given to mice every day for 8 weeks. Experimental parameters were monitored every two weeks (2, 4, 6, and 8 weeks) during the study period.

2.2. Preparation of SXF

The material used in this study, SXF, is an extract obtained from the fruiting bodies of Maitake mushroom (*Grifola frondosa*), provided by Mushroom Wisdom,

Inc. (East Rutherford, NJ). Briefly, SXF was prepared as follows:

Dried fruiting bodies, obtained from a mushroom farm (China), were first cut into 1 - 2 cm pieces and extracted with five volumes (w/w) of 95% ethanol at room temperature for 3 h. While the ethanol extract was removed by centrifugal filtration, the remaining residue was extracted with ten volumes of deionized water at 100˚C for 3 h. Following the aqueous extract was collected (by centrifugation), 95% ethanol was slowly added to it, achieving its final concentration of 50% - 75% (v/v). This mixture was maintained at 4˚C - 10˚C for 8 - 12 h to obtain the precipitate and floating material, which were then removed. The remaining supernatant was concentrated and dried, obtaining as a final product of SXF.

2.3. Experimental Design

As shown in Table 1, healthy, similar size/weight of 200 mice were randomized into five experimental groups (n = 40 per group): Group A (Sham), Group B (Orig-M), Group C [SXF (L)], Group D [SXF (H)], and Group E (ACT for Actos®). Actos® (Takeda Pharmaceuticals USA, Inc., Deerfield, IL) is the brand name of pioglitazone HCl, a medication used to treat Type 2 diabetes [20], and was included as a positive control) in this study. While food consumption with those materials was regularly monitored, body weight and several diabetic parameters were also measured every two weeks. In addition, blood was collected from the central large vein of 10 selected mice at each time period and subjected to the measurements of various serum parameters described below.

2.4. Serum Glucose Measurement

The serum glucose (GLC) level was measured using the LabAssay Glucose kit (Fujifilm Wako Pure Chemical Corp., Lexington, MA), which was based on the mutarotase-glucose oxidase (GOD) method. It is the enzymatic colorimetric assay measured at 505 nm on a microplate reader (Bio-Rad, Hercules, CA). The amount of glucose is determined using the standards and expressed by mg/dl. More details are described in the manufacturer's protocol.

2.5. 1,5-Anhydro-D-Glucitol

This 1,5-anhydro-D-glucitol (1,5-AG) is often used as a useful marker for assessing relatively short-term glycemic change [21]. The amount of 1,5-AG was measured using the 1,5-AG ELISA kit (MyBioSource, Inc., San Diego, CA). It is the Enzyme-Linked Immunosorbent Assay (ELISA), which is based on the antibody-antigen interaction. The amount of 1,5-AG was determined by the absorbance readings using a microplate reader and expressed by μg/ml. Detailed procedures are described in the vendor's protocol.

2.6. Serum Insulin

The serum insulin (INS) level was determined using the Insulin ELISA kit (Mercodia, Winston Salem, NC). The experimental procedures essentially followed the

manufacturer's protocol, and the amount of INS was determined and expressed by μg/l.

2.7. Serum Triglycerides

The amount of serum triglycerides (TGL) was measured using the Triglyceride Assay kit (Fujifilm Wako Pure Chemical Corp.), based on the GPO (glycerol-3-phosphatate oxidase-DAOS [*N*-Ethyl-*N*-(2-hydroxy-3-sulfopropyl)-3,5-dimethoxyaniline sodium salt] method. It was an enzymatic colorimetric (GPO-DAOS) method, and the absorbance readings of samples taken at 600 nm on a microplate reader were expressed by mg/dl. More details are described in the vendor's protocol.

2.8. Serum Total Cholesterol and High-Density Lipoprotein

The levels of serum total cholesterol (CHL) and high-density lipoprotein (HDL) in samples were measured using the Cholesterol E kit and the HDL-Cholesterol E kit (Fujifilm Wako Pure Chemical Corp.), respectively. The CHL measurement is based on an enzymatic colorimetric method, while the HDL measurement is on the immunoinhibition/precipitation method. The amount of CHL was determined by the absorbance readings of samples and expressed by mg/dl. For the HDL measurement, anti-lipoprotein antibody (in the reaction mixture) binds to several lipoproteins other than HDL, creating the antibody-antigen complexes that block other enzymatic reactions but allow specific enzymes to react only with HDL. This enzyme-HDL reaction then generates hydrogen peroxide that yields the blue color complex. After the absorbance readings were taken, the amount of HDL was calculated from the readings of the standards and expressed by mg/dl. Further details in both assays are described in the manufacturer's protocols.

2.9. Statistical Analysis

All data are presented as the mean ± SD (standard deviation), and statistical differences between groups are assessed with the Tukey-Kramer test after a one-way ANOVA. Values of $p < 0.05$ are considered to indicate statistical significance.

3. Results

3.1. Effect on Body Weight

Body weight of mice in all experimental groups gradually increased as time went by (**Figure 1**). It appears to be a normal trend, although a slight loss in body weight at 6 weeks was noticed despite continuing steady weight gain at 8 weeks. Thus, no materials given to mice had any effects on their body weight.

3.2. Effect on Serum Glucose (GLC) Levels

Possible effects of materials given to mice were examined on diabetic parameters, such as serum glucose (GLC), 1,5-anhydro-D-glucitol (1,5-AG), insulin (INS), triglycerides (TGL), total cholesterol (CHL), and high-density lipoprotein (HDL).

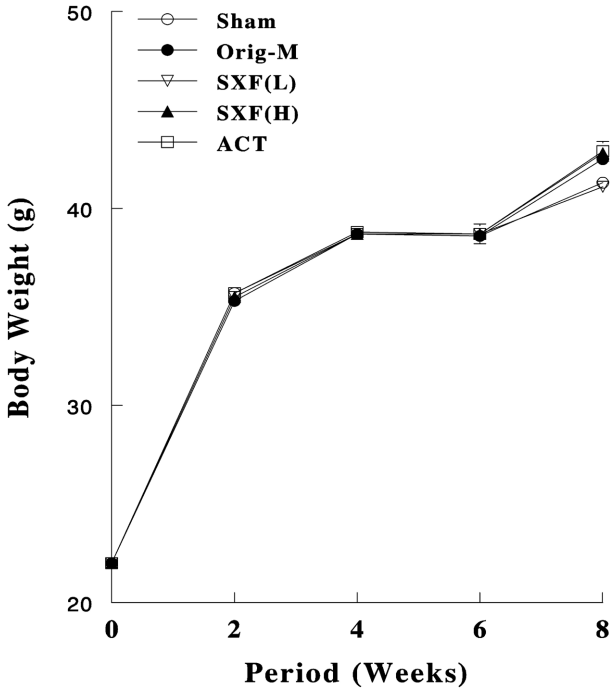

Figure 1. Effect on body weight. Experimental materials, Sham, Orig-M, SXF (L), SXF (H), or ACT, were consecutively given to mice for 8 weeks and body weight in all groups was measured at the given periods. All data are mean ± SD (standard deviation) from 10 selected mice per group.

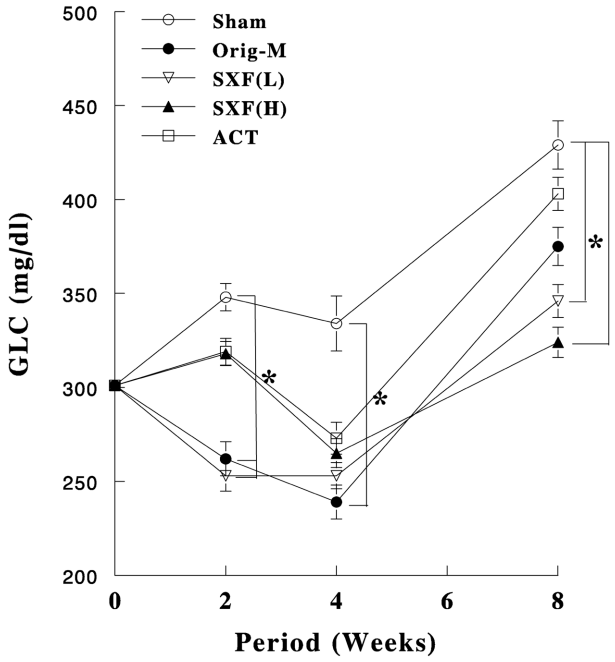

Figure 2. Effect on the serum glucose (GLC) level. The GLC levels in all groups were determined at the given periods as described in Materials and Methods. All data are mean ± SD from 10 selected mice per group (*$p < 0.05$ compared with Sham).

The GLC level in the Sham group was ~348 mg/dl at 2 weeks, while those mice received Orig-M or SXF (L) showed a significant decline ($p < 0.05$) in the GLC levels

of ~262 and ~254 mg/dl, respectively (Figure 2). At 4 weeks, the GLC of ~334 mg/dl was seen in the Sham group, but mice in the Orig-M group had a significant reduction ($p < 0.05$) to ~239 mg/dl. Although the GLC reduction with other materials was also found, it was not statistically significant. Finally, the Sham group had the GLC of 429 mg/dl at 8 weeks, while the SXF (L) and SXF (H) groups showed the significant decrease ($p < 0.05$) in the GLC of ~346 and ~324 mg/dl, respectively (Figure 2). Actually, these decreased GLC levels were yet *lower* than ~403 mg/dl seen in the ACT group. Therefore, these findings suggest that Orig-M, SXF (L), and SXF (H) have hypoglycemic effect, capable of lowering the GLC level, and they could be similarly or more effective than Actos®, a Type 2 diabetes drug clinically being used.

3.3. Effect on Serum 1,5-Anhydro-D-Glucitol (1,5-AG) Levels

Any effects on serum 1,5-AG was also examined because it has been used as a sensitive, day-to-day marker of short-term glycemic control (1-2 weeks) [21]. Despite changes in the GLC levels during the study periods, no significant changes in the 1,5-AG levels were found in any experimental groups (Figure 3). Hence, no materials had any distinctive effects on 1.5-AG.

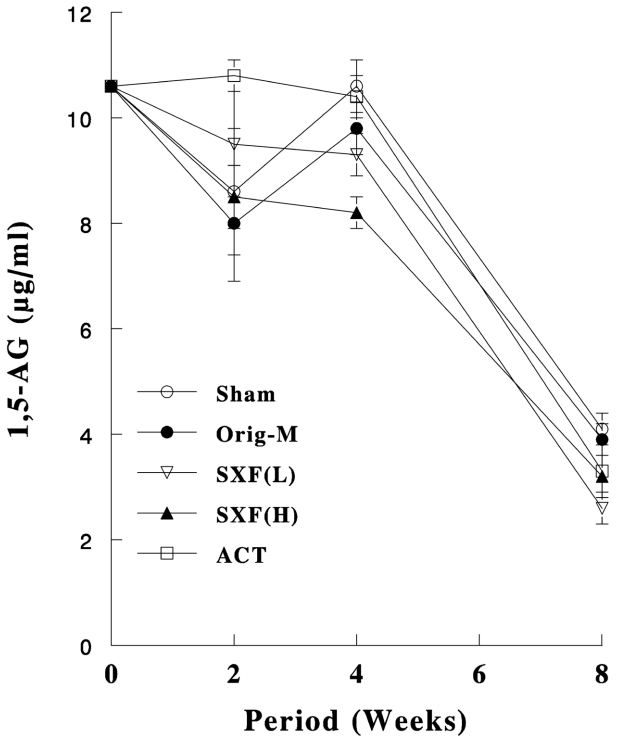

Figure 3. Effect on the serum 1,5-anhydroglucitol (1,5-AG) level. The 1.5-AG levels in all groups were determined, and all data are mean ± SD from 10 selected mice per group.

3.4. Effect on Serum Insulin (INS) Levels

The serum insulin (INS) levels kept slightly decreasing until the 8th week. The Sham group then had ~0.41 μg/l of INS, whereas the significant INS decline ($p < 0.05$) to ~0.24 μg/l was seen in the SXF (H) group at 8 weeks (Figure 4). The SXF

(L) group also showed distinctive ~0.29 μg/l of INS, although it was not yet statistically significant. Overall, these results suggest that SXF (L)/(H) might be capable of lowering the INS levels.

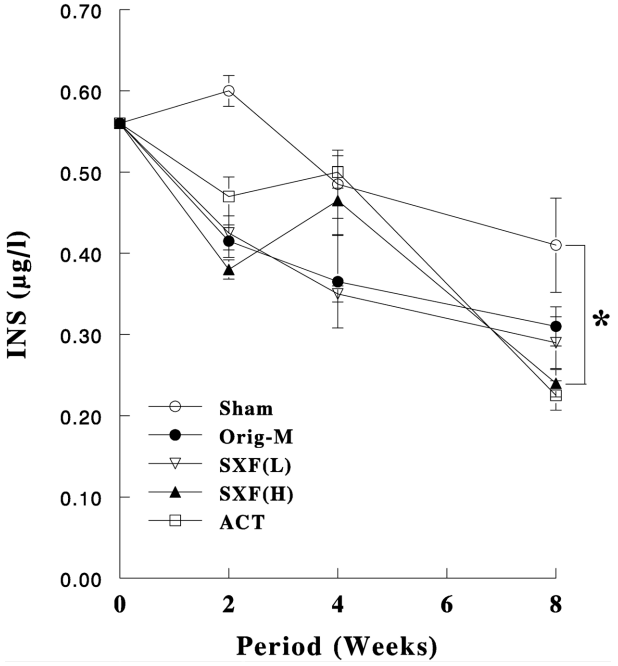

Figure 4. Effect on the serum insulin (INS) level. The INS levels in all groups were determined, and all data are mean ± SD from 10 selected mice per group (*$p < 0.05$ compared with Sham).

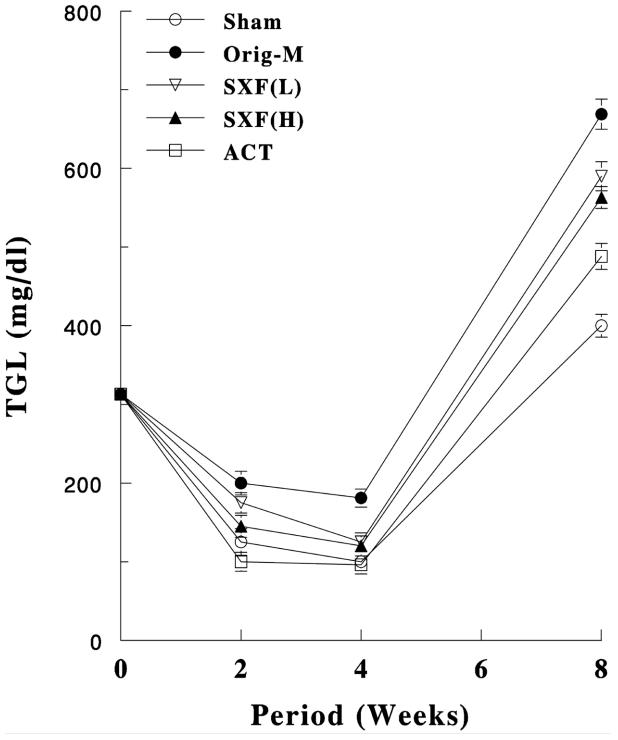

Figure 5. Effect on the serum triglycerides (TGL) level. The TGL levels in all groups were determined, and all data are mean ± SD from 10 selected mice per group.

3.5. Effect on Serum Triglycerides (TGL) Levels

Because of a potential link of diabetes to cardiovascular risk [22], the status of serum lipid parameters, such as triglycerides (TGL), total cholesterol (CHL), and high-density lipoprotein (HDL), were assessed. First, the TGL levels in the groups of Orig-M, SXF (L)/(H), and ACT were all *higher* than that of the Sham group (Figure 5). This suggests that the TGL levels may somewhat increase with those materials, although such elevated levels are not statistically significant.

3.6. Effects on Total Cholesterol (CHL) and High-Density Lipoprotein (HDL) Levels

The CHL levels in the materials given groups at 2 weeks were all considerably *higher* than that of the Sham group, which was significantly ($p < 0.05$) the lowest (Figure 6(a)). However, such high levels suddenly plunged and became closer to the Sham level at 4 weeks (Figure 6(a)). After this sudden fall, the CHL levels in those groups went up again at 8 weeks (higher than those at 2 weeks), although the Sham level yet remained the lowest (Figure 6(a)). Thus, similar to the finding of the TGL study, these results suggest that all materials given could have an insignificant effect on the CHL levels.

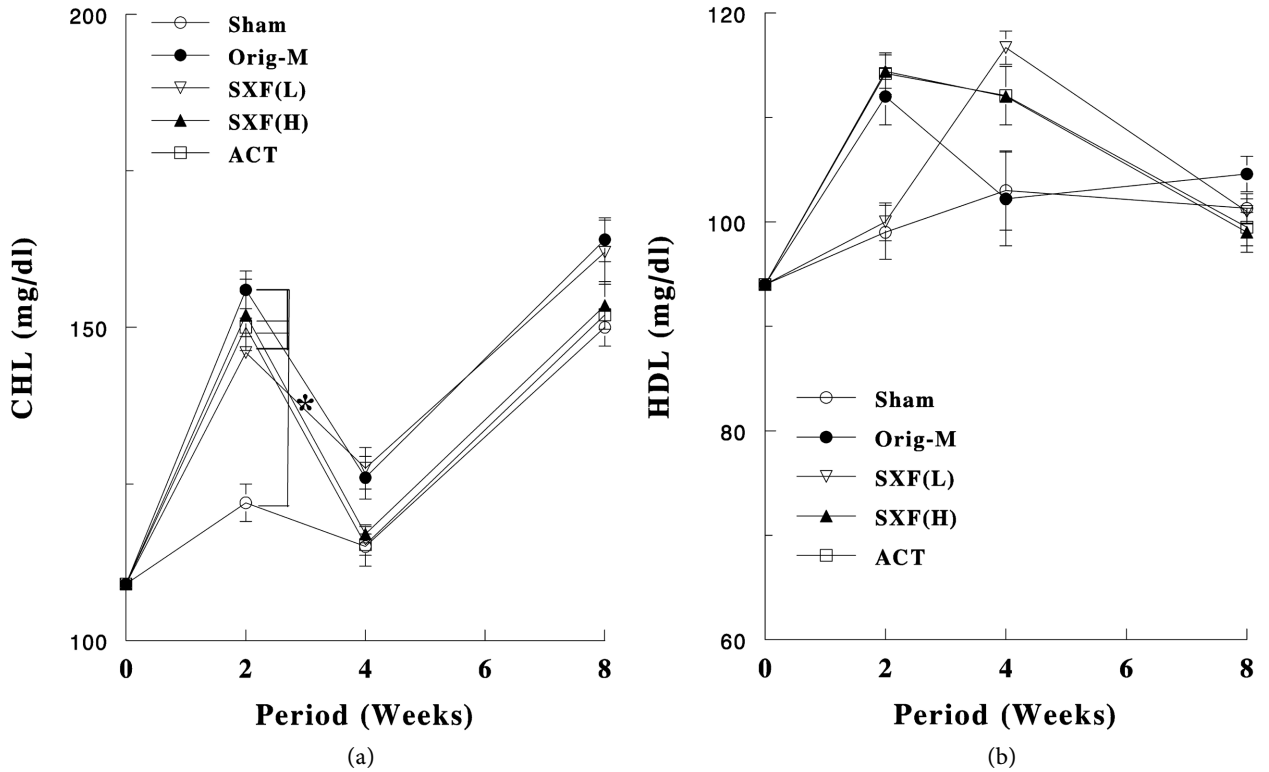

Figure 6. Effects on serum total cholesterol (CHL) and high-density lipoprotein (HDL). The CHL (a) and HDL (b) levels in all groups were determined, and all data are mean ± SD from 10 selected mice per group.

Lastly, although some different HDL levels were seen between the groups at 2 and 4 weeks (Figure 6(b)), such differences were not statistically significant. In

other words, no significant changes in the HDL levels were found between the groups throughout the experimental periods. Hence, materials given to mice appear to have no direct effect on the HDL levels.

4. Discussion

To find a safer and more effective option to treat diabetes, specifically Type 2 diabetes, we investigated if natural products, instead of ordinary medications, might have anti-diabetic activity to improve diabetic conditions. The natural bioactive extract, SX-fraction (SXF) obtained from maitake mushroom, was chosen to study its potential anti-diabetic activity in diabetic KK-A^{y} mice. We examined the effects of original/raw maitake mushroom powder, SXF (with the high or low dose), or Actos® (ACT) used as a reference drug, on several diabetic parameters in mice. Those included body weight, GLC, 1,5-AG, INS, TGL, CHL, and HDL, which were monitored and evaluated during the 8-week experimental period.

All mice in the 5 groups (Sham, Orig-M, SXF (H)/(L), and ACT) gradually gained weight and grew normally during a course of study. Hence, those different materials given to mice had little effects on their body weight or may not affect their overall metabolism.

We found that the GLC levels significantly declined with Orig-M or SXF (L)/(H), demonstrating the hypoglycemic effect (*i.e.*, the lowering of the GLC level). In fact, such a GLC decrease with SXF (L)/(H) was yet lower or better than that with Actos® (ACT) medication used as a reference. This is rather interesting and quite significant.

The 1,5-AG level was also examined because it was often used for assessing the short-term glycemic control [21] [23]. Actually, this 1,5-AG test has been commercially available since 1991 in Japan, and it is structurally similar to glucose but specifically the 1-deoxy form of glucose [24]. Because of such a structural similarity (to glucose), it has a physiological significance that the absorption of 1,5-AG is competitively inhibited by glucose in the kidneys (specifically renal tubules) [24]. Normally, nearly all of 1,5-AG filtered by the kidney will be reabsorbed, maintaining its consistent serum levels. However, when the serum glucose levels are high (in diabetic patients), the reabsorption of 1,5-AG is prevented by glucose, resulting in the excretion of 1,5-AG in the urine and thus decreasing its serum levels [23]. Hence, as soon as a rise in serum glucose occurs, 1,5-AG will fall immediately. This is why 1,5-AG is a useful marker for assessing the short-term glycemic control. Nevertheless, no significant 1,5-AG changes in the experimental groups were observed in this study.

Next, an elevation or increase in the INS level (hyperinsulinemia) is commonly seen in the early to mid-stage of Type 2 diabetic patients [25]. This is due to "insulin resistance" [8], a possible, primary cause of Type 2 diabetes, where insulin is overproduced (in the pancreas) to lower/control the elevated glucose levels. It is the compensatory mechanism for insulin resistance, resulting in the higher or increased insulin levels [25] [26]. Our study then showed that the INS levels were

somewhat fluctuated with those materials given. Particularly, the effects of SXF (H)/(L) were recognizable in the 8th week—the INS level was significantly lowered with SXF (H), while SXF (L) also distinctively lowered the level, although that was not statistically significant. Therefore, SXF (H)/(L) appear to effectively decrease or control the INS levels, at least in part demonstrating their anti-diabetic properties.

It was also important to address the effects of materials given on the cardiovascular parameters closely associated with diabetes [22]. We found that the levels of TGL, CHL, and HDL in the different groups were *not* significantly affected throughout the study period. However, it was rather surprised to see that the levels of both TGL and CHL in the materials-given groups were actually *higher* than that of the Sham group, while the HDL levels were nearly the same as that of the Sham. These findings are rather unexpected because the *reduced* TGL and CHL but the *elevated* HDL levels (with these given materials) would indicate the improved diabetic conditions. However, since such fluctuations in the TGL, CHL, and HDL levels are observable but *not* statistically significant, it remains uncertain whether they are truly the facts that should be considered and accepted. Hence, more studies might be required for further clarification.

After all, this study reveals the key finding that Orig-M and SXF are indeed capable of significantly lowering the GLC and INS levels in KK-A^y mice, demonstrating the anti-diabetic property, although little effects on serum lipid profile were found.

Moreover, it was also the interesting finding that the effects of SXF on GLC and INS appeared to be similar or more effective than Actos® (ACT) being clinically used today. Actos® (pioglitazone) belongs to the thiazolidinedione family and has been approved for the treatment of insulin resistance in Type 2 diabetes by the US FDA [20]. It promotes insulin sensitivity, improving the uptake of blood glucose through the peroxisome proliferator-activated receptor-gamma (PPARγ), ligand-activated transcription factors [27]. They play a key role in numerous metabolic processes, particularly glucose and lipid homeostasis. Pioglitazone is yet known to have side effects, such as fluid retention (peripheral oedema), cardiac hypertrophy, hypoglycemia etc. [28]. This thus suggests that SXF could be a safer and more effective alternative option.

Besides this animal study, we have also conducted the small, volunteer-based clinical study [29] to find the hypoglycemic (lowering GLC) effect of SXF, which was demonstrated in this mice study. Briefly, 10 patients took a SXF tablet (500 mg) three times a day for 4 weeks, and their fasting blood glucose (FBG) levels were measured *before* SXF intake (Day 0), at 2 weeks (Day 14), and *after* SXF trial (Day 28). These results are shown in **Table 2**.

All 10 patients showed a 30-63% decrease of FBG from an average FBG of ~205 mg/ml to that of ~116 mg/dl. That was an average of ~42.3% decline in their FBG levels under a SXF regimen in 2 to 4 weeks. The apparent FBG decreases were yet noticed in 2 weeks after the first SXF intake, and those values kept declining to 4

weeks. Moreover, none of participants presented palpable ailments or adverse effects related to SXF during the trial, confirming its safety even in human use. Although these results are encouraging and promising, more studies with more patients are certainly required for the further confirmation of hypoglycemic effect of SXF on Type 2 diabetic patients.

Table 2. Hypoglycemic effects of SXF on type 2 diabetic patients.

Patients	Age (yrs)	Sex	*Before* SXF* FBG (mg/dl)	*After* SXF*	% of FBG Declined with SXF
A	44	M	~260	90 - 100	~63
B	75	F	~200	110 - 130	~40
C	56	F	~220	120 - 130	~43
D	25	F	150-180	110 - 120	~30
E	60	M	~210	100 - 130	~45
F	37	M	180-200	120 - 140	~32
G	64	F	~220	130 - 150	~37
H	49	M	190-200	100 - 120	~41
I	41	M	~210	100 - 110	~50
J	53	F	170-190	100 - 110	~42
Mean	50.4	-	**~205**	**~116**	**~42.3**

**Before* and *After* SXF indicates the FBG values measured at Day 0 and Day 28, respectively. SXF: SX-fraction; FBG: fasting blood glucose; M: male; F: female.

Lastly, the legitimate question would be raised—how does SXF lower the GLC level? How does it work? Actually, we explored the hypoglycemic mechanism of SXF *in vitro*, using skeletal muscle cells [29]. We hypothesized that SXF might *activate* the insulin signal transduction (IST) pathway [30], overcoming *insulin resistance*, which is believed to be the primary cause of Type 2 diabetes. Briefly, the IST pathway involves the sequential events with several key regulators, starting from activation of insulin receptor (IR), insulin receptor substrate 1 (IRS-1), and protein kinase B (Akt) to translocation of glucose transporter type 4 (GLUT4). Once a cascade of signaling events was successfully completed, extracellular glucose will be transported to the (muscle) cell trough GLUT4, resulting in the *increased* glucose uptake and the decreased extracellular glucose level. It should be yet noted that the IR plays a critical role in the IST pathway because it is involved in a committed step, triggering the pathway [31]. Hence, (re)activation of IR with SXF could be the critical event, accounting for its underlying hypoglycemic mechanism to overcome insulin resistance.

5. Conclusion

The present study shows that maitake mushroom itself and its extract, SX-fraction

(SXF), have anti-diabetic activity in diabetic KK-A^y mice. Particularly, SXF demonstrated its anti-diabetic property, capable of lowering the serum glucose and insulin levels. However, SXF had little effects on other diabetic or lipid parameters in mice. Since the control of serum glucose and insulin levels is especially crucial in Type 2 diabetic patients, SXF may offer alternative anti-diabetic option with safety and efficacy. Further studies are thus warranted.

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Financial Disclosure

Financial support was generously provided by Mushroom Wisdom, Inc.

Author Contributions

Sensuke Konno: Conceptualization, Validation, Writing-Original Draft; Daniel Bassily: Investigation, Software; Charles White: Investigation, Data Curation; Sean Fullerton: Project administration, Data Curation; Cun Zhuang: Methodology, Resources, Supervision.

Data Availability

All data in this study are available from the corresponding author upon appropriate request.

Conflicts of Interest

The authors have no competing interest.

References

[1] Khan, M.A.B., Hashim, M.J., King, J.K., Govender, R.D., Mustafa, H. and Al Kaabi, J. (2020) Epidemiology of Type 2 Diabetes—Global Burden of Disease and Forecasted Trends. *Journal of Epidemiology and Global Health*, **10**, 107-111. https://doi.org/10.2991/jegh.k.191028.001

[2] Alper, J. (2000) New Insights into Type 2 Diabetes. *Science*, **289**, 37-39. https://doi.org/10.1126/science.289.5476.37

[3] Wagman, A.S. and Nuss, J.M. (2001) Current Therapies and Emerging Targets for the Treatment of Diabetes. *Current Pharmaceutical Design*, **7**, 417-450. https://doi.org/10.2174/1381612013397915

[4] Tiwari, D., Loh, W.J. and Aw, T.C. (2025) Updates from the 2025 American Diabetes Association Guidelines on Standards of Medical Care in Diabetes. *Exploration of Endocrine and Metabolic Diseases*, **2**, Article 101428. https://doi.org/10.37349/eemd.2025.101428

[5] American Diabetes Association (ADA) (2012) Standards of Medical Care in Diabetes 2011. *Diabetes Care*, **34**, S11-S63.

[6] Deshpande, A.D., Harris-Hayes, M. and Schootman, M. (2008) Epidemiology of Di-

abetes and Diabetes-Related Complications. *Physical Therapy*, **88**, 1254-1264. https://doi.org/10.2522/ptj.20080020

[7] Caro, J.F. (1990) Effects of Glyburide on Carbohydrate Metabolism and Insulin Action in the Liver. *The American Journal of Medicine*, **89**, S17-S25. https://doi.org/10.1016/0002-9343(90)90332-8

[8] Groop, L.C. (1999) Insulin Resistance: The Fundamental Trigger of Type 2 Diabetes. *Diabetes, Obesity and Metabolism*, **1**, S1-S7. https://doi.org/10.1046/j.1463-1326.1999.0010s1001.x

[9] Nolan, J.J., Ludvik, B., Beerdsen, P., Joyce, M. and Olefsky, J. (1994) Improvement in Glucose Tolerance and Insulin Resistance in Obese Subjects Treated with Troglitazone. *New England Journal of Medicine*, **331**, 1188-1193. https://doi.org/10.1056/nejm199411033311803.

[10] DeFronzo, R.A. and Goodman, A.M. (1995) Efficacy of Metformin in Patients with Non-Insulin-Dependent Diabetes Mellitus. *New England Journal of Medicine*, **333**, 541-549. https://doi.org/10.1056/nejm199508313330902

[11] Kubo, K., Aoki, H. and Nanba, H. (1994) Anti-Diabetic Activity Present in the Fruit Body of *Grifola frondosa* (Maitake). I. *Biological and Pharmaceutical Bulletin*, **17**, 1106-1110. https://doi.org/10.1248/bpb.17.1106

[12] Manohar, V., Talpur, N.A., Echard, B.W., Lieberman, S. and Preuss, H.G. (2002) Effects of a Water-Soluble Extract of Maitake Mushroom on Circulating Glucose/Insulin Concentrations in KK Mice. *Diabetes, Obesity and Metabolism*, **4**, 43-48. https://doi.org/10.1046/j.1463-1326.2002.00180.x

[13] Preuss, H.G., Echard, B., Bagchi, D., Perricone, N.V. and Zhuang, C. (2007) Enhanced Insulin-Hypoglycemic Activity in Rats Consuming a Specific Glycoprotein Extracted from Maitake Mushroom. *Molecular and Cellular Biochemistry*, **306**, 105-113. https://doi.org/10.1007/s11010-007-9559-6

[14] Mizuno, T. and Zhuang, C. (1995) Maitake, *Grifola frondosa*: Pharmacological Effects. *Food Reviews International*, **11**, 135-149. https://doi.org/10.1080/87559129509541024

[15] Adachi, K., Nanba, H. and Kuroda, H. (1987) Potentiation of Host-Mediated Antitumor Activity in Mice by *β*-Glucan Obtained from *Grifola frondosa* (Maitake). *Chemical and Pharmaceutical Bulletin*, **35**, 262-270. https://doi.org/10.1248/cpb.35.262

[16] National Cancer Institute (1992) Developmental Therapeutics Program. *In-Vitro* Anti-HIV Drug Screening Results (National Science Council F195001).

[17] Maitake Products Inc (1998) D-Fraction Obtained IND for Clinical Study (Corporate Publication).

[18] Tomino, Y. (2012) Lessons from the Kk-Ay Mouse, a Spontaneous Animal Model for the Treatment of Human Type 2 Diabetic Nephropathy. *Nephro-Urology Monthly*, **4**, 524-529. https://doi.org/10.5812/numonthly.1954

[19] Okazaki, M., Saito, Y., Udaka, Y., Maruyama, M., Murakami, H., Ota, S., *et al.* (2002) Diabetic Nephropathy in KK and KK-Ay Mice. *Experimental Animals*, **51**, 191-196. https://doi.org/10.1538/expanim.51.191

[20] Griggs, R.B., Donahue, R.R., Adkins, B.G., Anderson, K.L., Thibault, O. and Taylor, B.K. (2016) Pioglitazone Inhibits the Development of Hyperalgesia and Sensitization of Spinal Nociresponsive Neurons in Type 2 Diabetes. *The Journal of Pain*, **17**, 359-373. https://doi.org/10.1016/j.jpain.2015.11.006

[21] Yamanouchi, T. and Akanuma, Y. (1994) Serum 1,5-Anhydroglucitol (1,5 AG): New Clinical Marker for Glycemic Control. *Diabetes Research and Clinical Practice*, **24**,

S261-S268. https://doi.org/10.1016/0168-8227(94)90259-3

[22] Wong, N.D. and Sattar, N. (2023) Cardiovascular Risk in Diabetes Mellitus: Epidemiology, Assessment and Prevention. *Nature Reviews Cardiology*, **20**, 685-695. https://doi.org/10.1038/s41569-023-00877-z

[23] Dungan, K.M. (2008) 1,5-Anhydroglucitol (GlycoMark) as a Marker of Short-Term Glycemic Control and Glycemic Excursions. *Expert Review of Molecular Diagnostics*, **8**, 9-19. https://doi.org/10.1586/14737159.8.1.9

[24] Buse, J.B., Freeman, J.L.R., Edelman, S.V., Jovanovic, L. and McGill, J.B. (2003) Serum 1,5-Anhydroglucitol (GlycoMark): A Short-Term Glycemic Marker. *Diabetes Technology & Therapeutics*, **5**, 355-363. https://doi.org/10.1089/152091503765691839

[25] Cen, H.H., Hussein, B., Botezelli, J.D., Wang, S., Zhang, J.A., Noursadeghi, N., *et al.* (2022) Human and Mouse Muscle Transcriptomic Analyses Identify Insulin Receptor mRNA Downregulation in Hyperinsulinemia-Associated Insulin Resistance. *The FASEB Journal*, **36**, e22088. https://doi.org/10.1096/fj.202100497rr

[26] Morita, I., Tanimoto, K., Akiyama, N., Naya, N., Fujieda, K., Iwasaki, T., *et al.* (2017) Chronic Hyperinsulinemia Contributes to Insulin Resistance under Dietary Restriction in Association with Altered Lipid Metabolism in Zucker Diabetic Fatty Rats. *American Journal of Physiology-Endocrinology and Metabolism*, **312**, E264-E272. https://doi.org/10.1152/ajpendo.00342.2016

[27] Liu, C.H., Lee, T.H., Lin, Y.S., Sung, P.S., Wei, Y.C. and Li, Y.R. (2020) Pioglitazone and PPAR-γ Modulating Treatment in Hypertensive and Type 2 Diabetic Patients after Ischemic Stroke: A National Cohort Study. *Cardiovascular Diabetology*, **19**, Article No. 2. https://doi.org/10.1186/s12933-019-0979-x

[28] Lawrence, J.M. and Reckless, J.P.D. (2001) Actos (Pioglitazone): A New Treatment for Type 2 Diabetes. *Hospital Medicine*, **62**, 411-416. https://doi.org/10.12968/hosp.2001.62.7.1611

[29] Konno, S., Alexander, B., Zade, J. and Choudhury, M. (2013) Possible Hypoglycemic Action of SX-Fraction Targeting Insulin Signal Transduction Pathway. *International Journal of General Medicine*, **6**, 181-187. https://doi.org/10.2147/ijgm.s41891

[30] Saltiel, A.R. and Kahn, C.R. (2001) Insulin Signalling and the Regulation of Glucose and Lipid Metabolism. *Nature*, **414**, 799-806. https://doi.org/10.1038/414799a

[31] Khalid, M., Alkaabi, J., Khan, M.A.B. and Adem, A. (2021) Insulin Signal Transduction Perturbations in Insulin Resistance. *International Journal of Molecular Sciences*, **22**, Article 8590. https://doi.org/10.3390/ijms22168590