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# ANTIHYPERGLYCEMIC ACTIVITY OF *GANODERMA NEO-JAPONICUM* MUSHROOM IN OBESE/DIABETIC MICE

***Nguyen Quoc Cuong[1,*], Pham Van Phuc[2], Bui Thi Minh Dieu[1]***

[1] *Biotechnology Research and Development Institute, Can Tho University, Vietnam;*

[2] *Stem Cell Institute, University of Natural Sciences, Vietnam*

*Corresponding author: nguyenquoccuong.ma@gmail.com

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**Summary**

**Antihyperglycemic Activity of *Ganoderma neo-japonicum* Mushroom in Obese/Diabetic Mice**

The mushroom *Ganoderma neo-japonicum* is a new mushroom recently founded in Bu Gia Map National Park on the decomposing bamboo stump (*Schizostachyum* sp.). It has been studied on culturing, extracting active ingredients and medicinal properties in some countries such as Malaysia, Korea, Thailand, etc. The objective of this study was to investigate the antihyperglycemic effect of biomass extract (MasExt), fruit body extract (FrbExt), fruit body ganoderic acids (FrbGAs) and biomass ganoderic acids (MasGAs) in *Swiss albino obese*/diabetic mice. The obese mice (were fatted by High-Fat Diet) were induced with type 2 diabetes after dual dose streptozotocin (65mg/kg body weight) 5 days apart. The testing of blood glucose level (GL) in obese/diabetic mice showed that the hypoglycemic activity was present on all four types of active ingredients FrbGAs (↓68.3%GL), MasGAs (↓67.5%GL), MasExt (↓65.9%GL), FrbExt (↓51.6%GL). Thus, *G. neo-japonicum* mushroom has the hypoglycemic effect in obese mice with type 2 diabetes. In special, MasExt, MasGAs, FrbGAs help mice to better regulating blood glucose level and the amount of insulin in the blood. Addition, MasExt, MasGAs, FrbGAs are not only reduced blood glucose level but also reduced TC, LDL-c level in obese/diabetic mice.

**Keywords:** *Ganoderma neo-japonicum, Ganoderic acids, Type 2 diabetes, Biomass.*

## 1. Introduction

Bu Gia Map National Park in Binh Phuoc Province is a highly diverse nature reserve with many features of a tropical hilly ecosystem; there are many flora populations in which bamboo populations occupy a large area. The mushroom *Ganoderma neo-japonicum* is known on bamboo stump in Malaysia and has been found in Bu Gia Map National Park - Binh Phuoc in recent years.

*G. neo-japonicum* Imazeki (GNJI) have been known as lignin-degrading mushroom by Jo et al. [1]. It was then studied to improve the cellulose degradation activity by this same author's publication [2]. The culture process of *GNJI* mushroom was supplemented with methionine by Lee et al. [3] to effectively increase the production of ergothioneine and was supplemented with tryptophan by Park et al. [4] to increase the efficiency of phenolic compounds.

Antioxidant activity of *GNJI* had found with ethanol precipitation from the mycelia. [5],[6]. Active substances with strong antioxidant capacity cryptoporic acids H and I were reported by Lin et al.[7],[8] in fruit body. The ethanol precipitated fraction of Mushroom *Ganoderma neo-japonicum* mycelium was extracted and tested on 3T3-L cells by Subramaniam [9]; the results demonstrate this fraction has significant stimulated adipogenesis and exerted relatively mild anti-epinephrine induced lipolytic activities. Subramaniam showed that *G. neo-japonicum* may be useful as a potential therapeutic agent in the management of type 2 diabetes mellitus. Water extract of *GNJI* mushroom had a low ability to detoxify carbon tetrachloride-induced hepatotoxicity in rats. [7]

Therefore, this study aimed to further evaluate the effects of *G. neo-japonicum* collected from Bu Gia Map National Park in obese/diabetic mice caused by high-fat diet and streptozotocin as a type 2 diabetogenic agent.

## 2. Materials and methods

### Plant materials

*GNJI* fruit bodies in Bu Gia Map National Park were collected, washed, and dried at 45°C until there is no change in weight, finely ground, vacuum sealed and stored at room temperature. The process of morphological description and DNA sequencing for identification was carried out at the laboratory of the Institute of Biotechnology Research and Development, Can Tho University. *GNJI* biomass was harvested from the culture process (culture medium containing 90% rice, 5% cornstarch, 5% rice bran). These biomass samples and fruit bodies were harvested to produce extracts (fruit body extract, biomass extract) and ganoderic acids (fruit body ganoderic acids, biomass ganoderic acids) fraction which used to investigate the ability to stabilize blood glucose level in obese mice with type 2 diabetes.

The extract was prepared by extracting the mushroom sample in hot water at 90°C for 24 hours at a ratio of 1:10 (w/v), the extract then concentrated at 50°C until 50% volume remained, then adding 30% ethanol at ratio 1:1 (v/v), evaporated at 50°C to 50% volume, cooled at 2-5°C for 8 hours, remove precipitate, continue to evaporate at 50°C until 50% volume remained [10].

**Preparing ganoderic acids (GAs) fraction**

A gram of sample (biomass and fruit body) was suspended in 15 mL 70% ethanol (v/v). It was extracted two times; 24 hours each. After removing biomass with cellulose filter, the supernatant was dried at 50°C under vacuum condition. The residues were suspended by water and extracted with chloroform. The GAs in the chloroform phase was further extracted by 5% (w/v) $NaHCO_3$. The pH of $NaHCO_3$ phase was then adjusted to be lower than 3.0 by 2M HCl. Then GAs was extracted by chloroform and dissolved in ethanol after chloroform evaporated. The GAs quantity was measured at 245 nm using thymol as standard [11].

**Animals**

The male *Swiss albino* mice, 5-6 weeks old, average weight of 30 ± 2 g were provided by the Pasteur Institute in Ho Chi Minh City and allowed to stabilize for at least one week prior to testing.

**Model of causing type 2 diabetes in obese mice**

Mice were fed 100% High-Fat Diet (HFD) including: Asia feed A10S (commercial product) weaned pig food (protein 20% w/w, calcium 0.6% w/w, lysine 1.45% w/w, methionine + cystine 0.85% w/w) supplemented with bean oil 5% (w/w, commercial product) and cholesterol powder 1% (w/w, Merk) for 4 weeks. After fatting, diabetes was induced by intraperitoneal injection of streptozotocin (STZ, Merck) dissolved in 0.1M cold sodium citrate buffer, pH 4.0, at a dose of 45, 55, 65, 75 mg/kg. Mice were intraperitoneally injected STZ two doses on the first day and the fifth day at between 8.00-9:00 AM. On day 14 after second dose injection take blood samples to check blood glucose, total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c). Except for the difference in the injection of STZ, the care regimens were the same in all experimental groups.

**Intraperitoneal Glucose Tolerance Test (IPGTT) and Intraperitoneal Insulin Sensitivity Test (IPITT)**

The mice were fasted for 12h before starting the IPGTT with blood glucose measurement taken at 0 min. In IPGTT, the mice were then injected glucose load 2 g/kg bw from stock glucose 0.5 g/mL to conduct IPGTT. At 15-, 30-, 60- and 120-min following injection, the blood from the tail vein was collected to measure blood glucose levels using a portable glucometer. In IPIST, the mice were injected with human insulin at a dose of 0.75 UI/kg bw, and the process was conducted the same as IPGTT. Blood glucose levels from IPGTT and IPIST were processed with GraphPad Prism 9 software for calculating and analyzing about the area under the curve and total area under the curve (AUC).

**Experimental model to investigate the ability to stabilize blood glucose**

**Table 1.** Experimental arrangement to investigate the ability to stabilize blood glucose

| Groups | Experiment name | Impacted on mice |
|---|---|---|
| Control group | BlkCtrl | Normal mice were drinking distilled water, none HFD |
| | PosCtrl | Caused type 2 diabetes, treated with gliclazide 0.75 mg/kg bw |
| | NegCtrl | Caused type 2 diabetes without treatment |
| Treated group | MasExt | Caused type 2 diabetes, treated with MasExt 150 mg/kg bw |
| | FrbExt | Caused type 2 diabetes, treated with FrbExt 150 mg/kg bw |
| | MasGAs | Caused type 2 diabetes, treated with MasGAs 150 mg/kg bw |
| | FrbGAs | Caused type 2 diabetes, treated with FrbGAs 150 mg/kg bw |

** BlkCtrl: Blank control; PosCtrl: Possessive control; NegCtrl: Negative control; MasExt: Biomass extract; FrbExt: Fruit body extract; MasGAs: Biomass GAs; FrbGAs: Fruit body GAs*

Experimental mice were divided into two groups including control group and experimental group, each experimental batch consisted of 9 male mice. Except the blank control treatment, all mice were supplied HFD for 4 weeks and injected STZ 65 mg/kg bw 5 days apart to causing type 2 diabetes. The treatments were arranged as in ***Table 1*** and mice were

administered for 14 days. On the 14th day after taking the last dose, the mice were given no food for 8 hours, and then blood was taken from the heart to measure blood glucose, total cholesterol (TC), triglycerides (TG), HDL-cholesterol (HDL-c), and LDL-cholesterol (LDL-c).

**Quantification of Glucose, TC, TG, HDL-c, LDL-c in blood**

The blood samples were centrifuged and separated for serum and then the serum was quantified components TC, TG, HDL-c, LDL-c by automatic machine Olympus AU 2700, glucose was measured by ACCU check machine.

**Statistical analysis**

The experimental results were analyzed by statistical ANOVA and analyzed Area under the ROC (receiver operating characteristic) curve by GraphPad Prism 9 software.

## 3. Results and Discussion

**Model of causing type 2 diabetes in obese mice**

To induce type 2 diabetes in Wistar rats, Zhang [12] reported twice doses (30 mg/kg at weekly intervals for 2 weeks), Nath [13] administered 4 doses (160 mg/kg) per week apart in combination with a high-fat diet for 31 days to induce type 2 diabetes.

**Table 2.** Mice body weight during model of causing type 2 diabetes in obese mice

| Treatment | 0 day | 7 days | 14 days | 21 days | 28 days | 33 days | 40 days | 47 days |
|---|---|---|---|---|---|---|---|---|
| STZ0 | 30.4 ± 0.2 | 34.4 ± 0.2 | 37.8 ± 1.4 | 39.7 ± 1.6 | 41.6 ± 1.2 | 41.6 ± 1.6 | 42 ± 1.6 | 42 ± 0.8 |
| STZ45 | 31.2 ± 1.4 | 35.3 ± 2.1 | 38.8 ± 1.2 | 40.8 ± 1.4 | 42.7 ± 1.3 | 42.7 ± 2.0 | 43.6 ± 1.4 | 44 ± 1.6 |
| STZ55 | 30.9 ± 1.5 | 35 ± 1.8 | 38.5 ± 2.2 | 40.4 ± 0.8 | 42.3 ± 1.8 | 42.3 ± 0.6 | 42.3 ± 1.5 | 43.6 ± 1.0 |
| STZ65 | 31.1 ± 1.4 | 35.2 ± 2.1 | 38.7 ± 1.9 | 40.6 ± 0.7 | 42.6 ± 1.7 | 39.6 ± 3.3 | 40.4 ± 1.3 | 41.2 ± 1.3 |
| STZ75 | 30.3 ± 1.6 | 34.3 ± 0.6 | 37.7 ± 1.2 | 39.6 ± 2 | 41.5 ± 2 | Death | Death | Death |
| Blank control | 30.8 ± 1.6 | 32.9 ± 2.6 | 33.9 ± 1.8 | 35 ± 1 | 36.1 ± 1.4 | 36.2 ± 1.2 | 37 ± 1.4 | 37.9 ± 2.1 |

* Blank control (BlkCtrl): normal diet without adding bean oil and cholesterol.

Most of the mice administered STZ at dose of 160 mg/kg lost weight severely and died. In the experiment, at the end of the second injection of STZ at dose of 75 mg/kg for 5 days, more than 50% of obese mice died. In the remaining treatments, mice were still alive and developing normally.

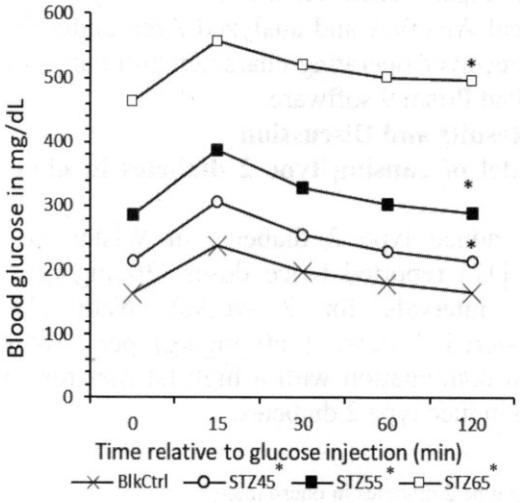
**Table 3.** Effect of STZ doses on biochemical parameters

| STZ (mg/kg) | Glucose (mg/dL) | TC (mg/dL) | TG (mg/dL) | HDL-c (mg/dL) | LDL-c (mg/dL) |
|---|---|---|---|---|---|
| 0 | $172.20^{d} \pm 8.40$ | $3.71^{b} \pm 0.09$ | $0.89^{a} \pm 0.03$ | $2.8^{a} \pm 0.11$ | $0.50^{c} \pm 0.02$ |
| 45 | $231.20^{c} \pm 15.63$ | $3.63^{b} \pm 0.05$ | $0.86^{a} \pm 0.08$ | $2.88^{a} \pm 0.07$ | $0.51^{c} \pm 0.04$ |
| 55 | $286.80^{b} \pm 15.33$ | $3.9^{b} \pm 0.16$ | $0.95^{a} \pm 0.05$ | $3.1^{a} \pm 0.10$ | $0.72^{b} \pm 0.07$ |
| 65 | $464.40^{a} \pm 19.15$ | $4.44^{a} \pm 0.19$ | $0.7^{b} \pm 0.01$ | $3.03^{a} \pm 0.08$ | $1.28^{a} \pm 0.06$ |
| 75 | Death | Death | Death | Death | Death |
| BlkCtrl | $163.60^{d} \pm 17.17$ | $2.85^{c} \pm 0.04$ | $0.49^{c} \pm 0.02$ | $2.5^{b} \pm 0.04$ | $0.25^{d} \pm 0.05$ |

* Symbol a, b, c, d after value is homogeneous groups in statistic ($P < 0.01$).

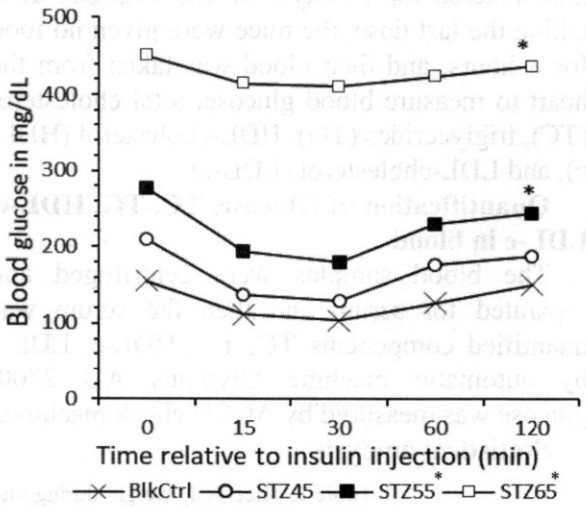
Two doses of STZ 65 mg/kg increased mouse blood glucose level to 464.6 mg/dL (>300 mg/dL, **Table 3**, $p < 0.01$). Mice injected at a STZ dose lower than 65 mg/kg normal alive, no weight loss, remained active, and ate well. Thus, after injecting dual dose of STZ 65 mg/kg, two doses 5 days apart caused a stable increase in blood glucose levels of mice up to 464.4 mg/dL. According to Wu et al. [14], animals will have chronic hyperglycemia and insulin resistance due to damaged and difficult recovery of β-cells when they are fortified with HFD and injected with STZ.

**Intraperitoneal glucose tolerance test (IPGTT) and intraperitoneal insulin sensitivity test (IPIST) of STZ dose survey**




(* is the difference group in ROC curve analysis)

**Fig. 1a.** Blood glucose levels in IPGTT after treated by STZ




(* is the difference group in ROC curve analysis)

**Fig. 1b.** Blood glucose levels in IPIST after treated by STZ

IPGTT results analyzed by Area under the ROC curve method (Fig. 1a) showed a significant increase in blood glucose in the three experimental groups ($p<0.05$). IPIST results analyzed by Area under the ROC curve method (Fig. 1b) showed a significant increase in blood glucose in the two experimental groups STZ55, STZ65 ($p<0.05$).

**Area under the ROC curve analysis of ITGTT, IPIST in obese/diabetic mice**

**Table 4.** Area under the ROC curve analysis of ITGTT, IPIST in causing type 2 diabetes model

| STZ mg/kg bw | ITGTT | | IPIST | |
|---|---|---|---|---|
| | Area | P value | Area | P value |
| 45 | 0.8800 ± 0.1224 | 0.0472 | 0.8400 ± 0.1329 | 0.0758 |
| 55 | 1.0000 ± 0.0000 | 0.0090 | 1.0000 ± 0.0000 | 0.0090 |
| 65 | 1.0000 ± 0.0000 | 0.0090 | 1.0000 ± 0.0000 | 0.0090 |

The result in Fig. 1a and Table 4 showed that blood glucose level in all groups (STZ45, STZ55, STZ65) increased in 15 minutes after glucose injection and then decreased after 120 minutes. At the time 120 minutes, blood glucose in all group reduced but they were higher than those in control group ($p<0.05$), this because of STZ was reported to disturb glucose homeostasis after glucose overload (2 g/kg wb) in obese [14]. In addition, the IPIST showed that (Fig. 1b, Table 4), the blood glucose levels of mice at group STZ55, STZ65 were significantly different from those of the control ($p<0.05$). After 30 minutes of insulin injection, the blood glucose level in the control groups, STZ45, STZ55 decreased to 33-35%, and 9% in STZ65. Thereby, when STZ treated with a dose of 65 mg/kg bw, insulin intolerance was recorded, which is the basic sign to recognize type 2 diabetes [14].

**Investigate the ability to stabilize blood glucose in obese/diabetic mice after 14 days treatment**

**Table 5.** Monitor blood glucose level in obese/diabetic mice during 14 days of treatment

($P < 0.05$)

| Treatment | 0 day (mg/dL) | 7 days (mg/dL) | 14 days (mg/dL) |
|---|---|---|---|
| BlkCtrl | 161.3 ± 7.3 | 157.3 ± 30.8 | $156.0^{ab}$ ± 10.0 |
| NegCtrl | 463.3 ± 10.4 | 486.7 ± 1.3 | $463.0^{e}$ ± 8.3 |
| PosCtrl | 443.7 ± 13.4 | 373.0 ± 13.1 | $237.7^{d}$ ± 7.6 |
| MasExt | 436.7 ± 6.7 | 344.0 ± 4.6 | $157.7^{ab}$ ± 12.5 |
| FrBExt | 416.0 ± 10.6 | 391.3 ± 14.8 | $224.0^{cd}$ ± 12.3 |
| MasGAs | 447.3 ± 18.7 | 334.7 ± 10.5 | $150.6^{a}$ ± 9.2 |
| FrBGAs | 455.6 ± 14.7 | 334.0 ± 7.7 | $146.7^{a}$ ± 5.2 |

* Symbol a, b, c, d after value is homogeneous groups in statistic ($P < 0.01$)

The results showed that the test substances had a significant blood glucose lowering effect ($p<0.05$) in Table 5 specifically: biomass GAs (reduced by 67.5%), fruit body GAs (reduced 68.7%), biomass extract (down 65.9%), fruit body extract (reduced 51.6%). Biomass GAs, fruit body GAs, biomass extract gave no different results compared to blank control, showing that GAs is a group of substances with have efficiency in lowering blood glucose of mice. At the same time, fruit body extract is lower effect than biomass extract, this may have different substances in biomass extract and fruit body. The antihyperglycemic activity of the investigated compounds were generally higher than that of polysaccharides from *G. lucidum* (reducing blood glucose 31.8%) [15] and ethanol extract of *G. lucidum* (decrease blood glucose 63.94%) [16].

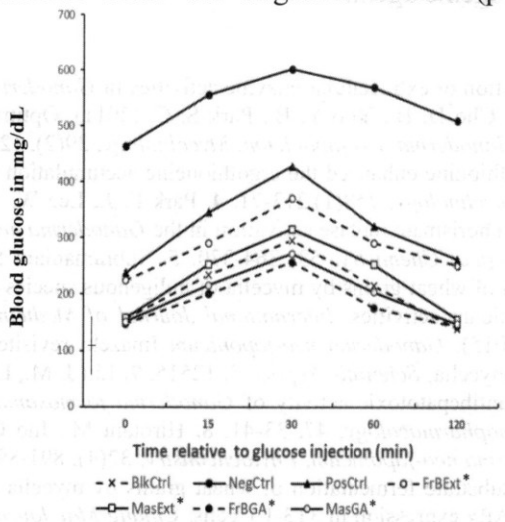
**Area under the ROC curve analysis of ITGTT, IPIST in obese/diabetic mice after 14 days treament**

**Table 6.** Area under the ROC curve analysis of ITGTT, IPIST in obese/diabetic mice after 14 days treatment

| Treatment | ITGTT | | IPIST | |
|---|---|---|---|---|
| | Area | P value | Area | P value |
| PosCtrl | 1.000 ± 0.0000 | 0.0001 | 1.0000 ± 0.0000 | 0.0001 |
| MasExt | 1.000 ± 0.0000 | 0.0001 | 1.0000 ± 0.0000 | 0.0001 |
| FrbExt | 1.000 ± 0.0000 | 0.0001 | 1.0000 ± 0.0000 | 0.0001 |
| MasGAs | 1.000 ± 0.0000 | 0.0001 | 1.0000 ± 0.0000 | 0.0001 |
| FrbGAs | 1.000 ± 0.0000 | 0.0001 | 1.0000 ± 0.0000 | 0.0001 |

The results of IPGTT, IPIST in obese/diabetic mice are shown in Fig. 2a-b and analyzed by the Area under the ROC curve method (Table 6). The results of ROC curve analysis showed that the four experimental compounds were significantly different from the negative control ($p<0.01$, Table 6).

**Intraperitoneal Glucose Tolerance Test (IPGTT) and Intraperitoneal Insulin Sensitivity Test (IPIST) in obese/diabetic mice induced type 2 diabetes and 14 days of treatment**




(* is the difference group in ROC curve analysis)

**Fig. 2a.** Blood glucose levels in IPGTT after 14 days treatment

(* is the difference group in ROC curve analysis)

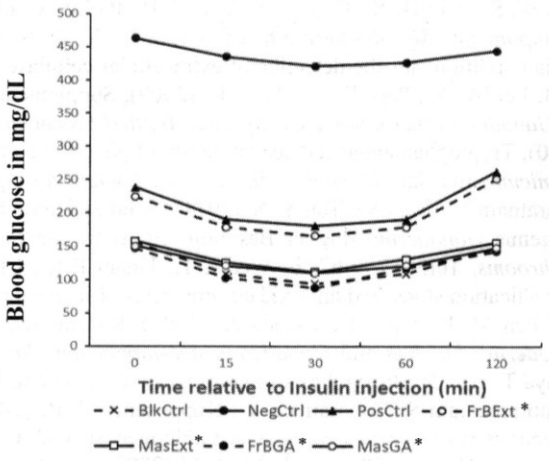



**Fig. 2b.** Blood glucose levels in IPIST after 14 days treatment

The IPGTT experiment (Fig. 2a) showed that blood glucose levels of mice in biomass extract, biomass GAs, fruit body GAs and blank control groups could return to almost the initial level. Thus, biomass extract, biomass GAs and fruit body GAs can help the obese/diabetic mice regulate blood glucose level well after glucose overload. Fruit body extract was helping the mice body regulate blood glucose level, but it was lower effect than biomass extract, biomass GAs and fruit body GAs.

The IPIST results (Fig. 2b) showed that the mice in biomass extract, biomass GAs, fruit body GAs and blank control groups had a sharp decrease in blood glucose after 30 min of insulin injection and then returned to almost the initial levels, indicating that these test extracts ameliorate the insulin resistant. Fruit body extract

also showed the lowest improving effect on insulin sensitivity, like the results of Fig 2a.

**Quantification of TC, TG, HDL-c, LDL-c in in obese/diabetic mice blood serum after 14 days of treatment**

**Table 7.** Quantification of TC, TG, HDL-c, LDL-c after 14 days of treatment ($P < 0.05$)

| Treatment | TC (mg/dL) | TG (mg/dL) | HDL-c (mg/dL) | LDL-c (mg/dL) |
|---|---|---|---|---|
| BlkCtrl | $2.85^{a} \pm 0.04$ | $0.5^{a} \pm 0.01$ | $2.5^{a} \pm 0.05$ | $0.25^{a} \pm 0.02$ |
| NegCtrl | $4.44^{e} \pm 0.19$ | $0.7^{b} \pm 0.01$ | $3.03^{bc} \pm 0.08$ | $1.28^{d} \pm 0.06$ |
| PosCtrl | $4.16^{de} \pm 0.16$ | $1.17^{e} \pm 0.09$ | $3.31^{d} \pm 0.09$ | $0.61^{b} \pm 0.05$ |
| FrBExt | $4.14^{cde} \pm 0.13$ | $1.17^{e} \pm 0.09$ | $3.31^{d} \pm 0.09$ | $0.61^{b} \pm 0.04$ |
| MasExt | $3.80^{bc} \pm 0.04$ | $0.94^{cd} \pm 0.06$ | $3.02^{bc} \pm 0.08$ | $0.66^{bc} \pm 0.03$ |
| FrBGAs | $3.60^{b} \pm 0.04$ | $0.78^{bc} \pm 0.06$ | $2.85^{b} \pm 0.06$ | $0.59^{b} \pm 0.03$ |
| MasGAs | $4.08^{cd} \pm 0.11$ | $1.08^{de} \pm 0.09$ | $3.2^{cd} \pm 0.15$ | $0.77^{c} \pm 0.03$ |

* Symbol a, b, c, d after value is homogeneous groups in statistic ($P < 0.01$)

Table 7 showed that the serum TC and LDL-c levels in obese/diabetic mice treated with either biomass extract, fruit body GAs, or biomass GAs were significantly reduced as compared with negative control ($p<0.05$). Huang et al. reported that the improvement of dyslipidemia in type 2 diabetic rats fed with high-cholesterol diets by *G. lucidum* may be through regulating lipid synthetic/metabolic enzyme activities and lipid excretion. The advance study on hepatic acetyl-CoA carboxylase, fatty acid synthase or lipoprotein lipase is necessary for further mechanism of G. neo-japonicum effect in obese/diabetic mice [17].

## 4. Conclusion

Biomass extract, fruit body GAs, and biomass GAs of *G. neo-japonicum* collected from Bu Gia Map National Park showed the modulating effect on glucose overload, ameliorating effect on insulin resistance, and decreasing triglycerides and LDL-c levels in obese/diabetic mice caused by high-fat diet and streptozotocin as a type 2 diabetogenic agent.

**Reference**


**1.** Jo W. S., Park H. N., Cho D. H., Yoo Y. B., Park S. C. (2000), Detection of extracellular enzyme activities in *Ganoderma neo-japonicum*, *Mycobiology,* 39(2),118-120. **2.** Jo W. S., Park H. N., Cho D. H., Yoo Y. B., Park S. C. (2011), Optimal media conditions for the detection of extracellular cellulase activity in *Ganoderma neo-japonicum*, *Mycobiology*, 39(2), 129-32. **3.** Lee W. Y., Park E. J., Ahn J. K. (2009), Supplementation of methionine enhanced the ergothioneine accumulation in the *Ganoderma neo-japonicum* mycelia, *Applied Biochemistry and Biotechnology, 1*58(1),213-21. **4.** Park E. J., Lee W. Y. (2010), Tryptophan enhanced accumulation of phenolic compounds via chorismate mutase activation in the *Ganoderma neo-japonicum* mycelia, *Journal of the Korean Society for Applied Biological Chemistry,* 53, 364-370. **5.** Subramaniam S., Sabaratnam V., Rani K., Tan Y. S. (2014), Solid-substrate fermentation of wheat grains by mycelia of indigenous species of the genus *Ganoderma* (higher Basidiomycetes) to enhance the antioxidant activities, *International Journal of Medicinal Mushrooms,* 16(33),259-67. **6.** Wee C.T., Umah R.K., Chia W.P. (2015), *Ganoderma neo-japonicum* Imazeki revisited: Domestication study and antioxidant properties of its basidiocarps and mycelia, *Scientific Repots*, 5, 12515. **7.** Lin J. M., Lin C., Chen M. F., Ujiie T., Takada A. (1995), Radical scavenger and antihepatotoxic activity of *Ganoderma formosanum, Ganoderma lucidum* and *Ganoderma neo-japonicum, Journal of Ethnopharmacology*, 47, 33-41. **8.** Hirotani M., Ino C., Furuya T. (1993), Biosynthesis of cryptoporic acids H and I in *Ganoderma neo-japonicum*, *Phytochemistry,* 32(4), 891-896. **9.** Subramaniam S., Sabaratnam V., Kuppusamy U. R. (2014), Solid-substrate fermentation of wheat grains by mycelia of indigenous *Ganoderma spp.* enhanced adipogenesis and modulated PPARγ expression in 3T3-L1 cells, *Chiang Mai Journal of Science,* 41, 1-13. **10**. Nguyễn Minh Tú (2009), Quy trình chiết tách các hoạt chất sinh học từ Linh chi *G. lucidum*, *Tạp chí Khoa học và Công nghệ*, 1, 45-53. **11**. Fang Q.H., Zhong J.J. (2002), Effect of initial pH on production of ganoderic acid and polysaccharide by submerged fermentation of *G. lucidum*, *Process Biochemistry*, 37 (7), 769-774. **12**. Zhang M., Lv X.Y., Li J., Xu Z.G., Chen L. (2008), The characterization of high-fat diet and multiple low-dose streptozotocin induced type 2 diabetes rat model, *Experimental diabetes research*, Article ID 704045, 1-9. **13**. Nath S., Ghosh S.K., Choudhury Y. (2017), A murine model of type 2 diabetes mellitus developed using a combination of high fat diet and multiple low doses of streptozotocin treatment mimics the metabolic characteristics of type 2 diabetes mellitus in humans, *Journal of pharmacological and toxicological methods*, 84, 20-30. **14**. Wu J., Yan L.J. (2015), Streptozotocin-induced type 1 diabetes in rodents as a model for studying mitochondrial mechanisms of diabetic β cell glucotoxicity, *Diabetes, metabolic syndrome and obesity: targets and therapy*, 8, 181-188. **15**. Zhang H.N., Lin Z.B. (2004), Hypoglycemic effect of *G. lucidum* polysaccharides, *Acta Pharmacologica Sinica*, 25 (2), 191-195. **16**. Ratnaningtyas N.I., Hernayanti H., Andarwanti S., Ekowati N., Purwanti E.S., Sukmawati D. (2018), Effects of *G. lucidum* extract on diabetic rats, *Biosaintifika: Journal of Biology & Biology Education*, 10 (3), 642-647. **17.** Huang C.H., Lin W.K., Chang S.H., Tsai G.J. (2021), *G. lucidum* culture supplement ameliorates dyslipidemia and reduces visceral fat accumulation in type 2 diabetic rats, *Mycology*, 12 (2), 94-104.