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ORIGNAL PAPER

The effect of ginger extract ingestion and swimming exercise on insulin resistance and skeletal muscle antioxidant capacity and apoptosis in hyperglycemic rats fed a high-fructose diet

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Abstract

This study purposed to examine the effects of ginger extract and swimming exercise administered to hyperglycemic rats on their insulin resistance, antioxidant ability and apoptosis. For this purpose, we divided 40 15-week-old male SD rats with induced hyperglycemia into control group (CON), exercise group (EX), ginger extract group (GI), and ginger extract + exercise group (GI+EX), and through 8 weeks' experiment we performed weight, blood glucose, insulin concentration, HOMA-IR, SOD activity, TBARS content and apoptosis of gastrocnemius muscle. Body weight was not significantly different among the groups. Blood glucose changed significantly over time in GI and GI-EX. Insulin concentration decreased significantly over time in GI and GI-EX, and was significantly lower in GI-EX among the groups. HOMA-IR decreased significantly over time in EX, GI and GI-EX, and was significantly lower in GI-EX among the groups. Among time points x groups, significant difference was observed in GI-EX at time points 2, 3 and 5. As to the antioxidant ability of gastrocnemius muscle, SOD activity and TBARS content were not changed by ginger extract and exercise, and apoptosis. No significant difference was observed in apoptotic factors P53 and caspase-3, anti-apoptotic factors Bcl-2 among the groups. Accordingly, the administration of ginger extract and exercise are expected to lower blood glucose and prevent diabetes and hyperglycemia, antioxidant capacity and apoptosis in the additional study is necessary.

Keywords: hyperglycemia, ginger, antioxidant, apoptosis, swimming exercise

INTRODUCTION

Hyperglycemia has been reported to promote the production of reactive oxygen species (ROS) like hydroxy radical [1]. Abnormal glucose metabolism causes mitochondrial phosphorylation and NADPH/NADP ratio change. In particular, abnormal metabolism in mitochondria and ROS (reactive oxygen species) production by NAD(P)H oxidase activation have drawn attention [2-4]. ROS production has been known to activates cellular oxidative stress, resulting in MAPKs (mitogen-activated protein kinases) increase, and to play an important role in producing JNK(c-Jun amino (N)-terminal kinase) and p38 that induce apoptosis [5]. ROS production caused the oxidative disorder of mitochondrial membrane, activating caspase-8 and caspase-9 that play an important role in apoptosis through caspase-3 [6]. The vessel expansion of the soleus muscle during exercises produced ROS and increased NO (nitric oxide) [7]. exercise produced ROS, resulting in increasing apoptosis due to mitochondrial functional disorders in the skeletal muscle. an appropriate exercise has been reported to prevent hyperglycemia and reduce oxidative stress, resulting in the activity reduction of apoptosis factors and apoptosis delay [8,9]. However, as negative effects of exercise have been reported in some cases, an interest in medicinal herbs has been increasing as an alternative to exercise for maintaining health along with a trend in functional food intake for prevention. Phytochemical included in herbs and plants has been reported to have a function of anti-diabetes and anti-apoptosis [10-12]. Ginger, which was used in this study, has been known to contain

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an approximately 1-4% of volatile oil in the root, and be abundant in zingiberene, bisabolene, gingerols, and shogaols [13]. It had been known to have pharmaceutical functions such as removal of fever, antibacterial, liver improvement, diuretic effect, hyperglycemia, hypercholesterolemia), antistress, antioxidation, and adiponectin activity increase [14,15]. Ginger extract significantly reduced glucose and proteinuria levels, leading to the reduction of blood cholesterol, triglyceride, and insulin, and the improvement of hyperglycemia and hyperinsulinemia, which was effective in anti-diabetes [16,17]. Treatment of 6-gingerol in mouse macrophages inhibited both NO and ROS, and had potent antioxidant and anti-inflammatory actions as well as anti-apoptosis *in vivo* and *in vitro* studies [18,19]. However, studies on the effect of the combinational treatment of ginger extract and exercise on the antioxidant capacity and anti-apoptosis in the skeletal muscle have been insufficiently conducted.

Accordingly, this study was conducted to investigate the effect of swimming exercise and ginger extract on insulin resistance and the antioxidant capacity and anti-apoptosis in the skeletal muscle in hyperglycemic rats.

STUDY METHODS

Laboratory animal feeding

In this study, 40 SD (Sprague-Dawley) male rats aged 4 weeks were used. Each rat was individually housed in a cage. The internal environment of the cage was maintained at temperature 23-25℃, relative humidity 60%, and light/dark cycle for 08:00~20:00 with 12-hour interval. Hyperglycemic rats aged 15 weeks were divided into four groups according to randomized block design: control group (CON), exercise group (EX), ginger extract group (GI), ginger extract+exercise group (GI-EX). For feeding, high-fructose diet based on AIN-76 was provided to rats during the study period by referring the dietary composition table suggested by [20]. Water and food were freely provided. The dietary composition was presented in Table 1.

Table 1. Composition of experimental diets (total : 100%)

Ingredient	High-fructose diet
corn starch	50
fructose	21
casein	14
corn oil	6
lard	4
mineral mix*	3.5
vitamin mix*	1.0
DL-methionine	0.3
choline	0.2

* mineral mix, vitamin mix: AIN-76

Ginger extraction and administration

Ginger 2.1㎏ was washed and dried, and then extracted with a juice extractor. Distilled water 2 L and ethanol 8 L were added to the extract, followed by heating. The ginger extract was put into EYELA concentrator (Japan) for 7-hour concentration to obtain ginger extract. A 100 ㎎/㎏ of ginger extract was orally administered by referring [21]. The ginger extract was administered to the exercise group after exercise and to the non-exercise groups in stable condition. Saline solution was the same dose was administered to the control group once a day.

Change in glucose concentration during the study

Blood was collected from the orbit every other week in 6-hour fasting condition during feeding period, and was measured using a blood glucose analyzer (Glucodcotor, AGM-2100) to check hyperglycemia [22]. Blood which was collected from 15-week old stage, time of hyperglycemia induction with an interval of 2 weeks, was put into a tube treated with heparin, and was centrifuged at 700 × g. the plasma was then stored in a deep freezer at -70℃.

Exercise methods

Exercise was taken from 15-week old stage, the time of hyperglycemia induction for 8 weeks. Water temperature was maintained at 35 ± 1℃ in a circular water pool with depth 50 cm and radius 25 cm. Swimming was exercised five times a week. The exercise was taken for 10 minutes at first trial, and gradually increased for adaptation. The swimming was exercised for 60 minutes from 3~8 week.

Sample collection

Under 12-fasting condition, the rat abdomen was opened under anesthesia with ether. Blood was collected from the abdominal aorta, and was centrifuged at 700 × g for 15 minutes. The samples were stored in a freezer before analysis. for the analysis of antioxidation and apoptosis, the gastrocnemius was taken. After clamping, its weight was measured after its activity was halted in liquid nitrogen, followed by storage in a -70℃ deep freezer.

Items and methods of analysis

Insulin

Insulin concentration in the blood was measured using RIA kit (LINCO Research Cat# RI-13K) and *r*-counter (1470 Wizard, Wallac, Automatic Count, Finland). Homeostasis model assessment of insulin resistance (HOMA-IR) was used to assess insulin resistance.

HOMA-IR = {plasma insulin (ng/ml) / 0.0417 × blood glucose (mg/dl)}/2430

Gastrocnemius antioxidation

For SOD activity, gastrocnemius 100 mg was taken and washed with phosphate buffered saline (PBS, pH 7.4). Then, it was mixed with HEPES buffer, EGTA, mannitol, and sucrose to make its pH level 7.2. Pretreatment solution 1ml and the sample were added and then irradiated with sonicate. The supernatant was used after centrifugation as 1,500 × g for four minutes. In addition, for TBARS concentration, gastrocnemius 100mg was taken and treated with RIPA buffer and PMSF, followed by irradiation in a sonicate. After centrifugation at 1,600 × g, the supernatant was taken and used. SOD activity (Cayman, Cat# 706002, USA) and TBARS concentration (Cayman, Cat# 10009055, USA) were measured using enzyme-linked immunosorbent assay.

Western blot of p53, bcl-2, bcl-xl, and caspase-3 in the gastrocnemius

For the analysis of apoptosis mechanism, the gastrocnemius was pretreated and its protein was then quantified using bicinchoninic (BCA) protein assay kit (Bio-Rad, USA). For protein separation, each protein sample was loaded onto 15% SDS-PAGE gel, followed by electrophoresis. After protein separation, the sample was transferred into PVDF membrane, and underwent blocking for one and half hour using blocking buffer (5% skim milk in PBS). Primary antibodies such as p53, Bcl-2 (Santa Cruz, USA), Bcl-xl (Cell Signaling, USA), and caspase-3 (Cell Signaling, USA) were diluted and mixed with the sample for two hours, followed by 10 min-wash with PBS (5% tween-20) five times. Secondary antibodies were diluted and mixed with the sample for one hour, followed by 10min-wash with PBS (5% tween-20) five times. For the identification of protein bands, the membrane was illuminated with enhanced chemiluminescence (ECL) kit and developed in x-ray film, the band density was analyzed using a densitometry (Bio-Rad, U.S.A).

Data processing

For all the results of this study, the mean and the standard deviation were calculated using SPSS 17.0 software. One-way ANOVA with repeated measures was conducted for blood glucose, insulin, and HOMA-IR, whereas one-way ANOVA was conducted for weight, and the antioxidation and apoptosis in the skeletal muscle. A back-testing was conducted using LSD (least significant difference). Significance level for hypothesis testing was set as $p < .05$.

STUDY RESULTS

Change in weight

For weight change for 8 weeks after hyperglycemia induction during a total of 22-week feeding period, the weight change was shown to increase from 498.5 g to 552.7 g in the CON, from 488.1 g to 525.6 g in the EX, from 483.2 g to 556.7 g in the GI, and from 480.9 g to 526.2 g in the GI-EX. In addition, the weight was shown to increase by 10.7% in the CON, 7.5% in the EX, 14.7% in the GI, and 9.0% in the GI-EX, which showed no statistical significant difference <Fig. 1>.

Change in blood glucose, insulin and HOMA-IR

No statistically significant difference in blood glucose was found between periods × groups, but a significant difference was shown in the GI and GI-EX groups ($p < .01$) <Table. 2>. Insulin change was shown to significantly decrease in the GI and GI-EX groups for period ($p < .01$), and in the GI-EX group between the groups ($p < .01$), but no statistically

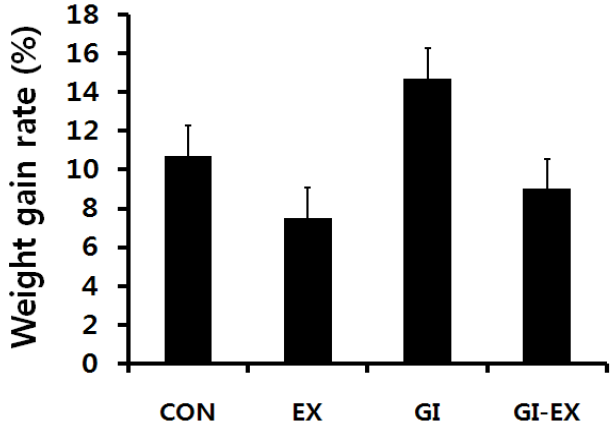

Fig. 1. Changes of weight gain rate in each group. Bars are mean ± SE. CON: control + sedentary; EX: control + exercise; GI: ginger; GI-EX: ginger + exercise

Table 2. The changes of blood glucose concentration

		CON	EX	GI	GI-EX	source	*F*	*p*
Blood glucose (mg/dl)	1st	177.42 ± 17.31	177.71 ± 16.52	177.71 ± 16.86	177.28 ± 18.06			
	2nd	186.28 ± 13.88	185.28 ± 12.20	185.28 ± 8.22	187.57 ± 17.27	time	25.796	.000**
	3th	170.57 ± 21.06	148.42 ± 6.29	154.71 ± 15.12	152.85 ± 10.89	group	2.965	.052
	4th	167.71 ± 12.14	153.14 ± 6.611	166.42 ± 12.67	151.71 ± 7.95	time vs group	14.00	.179
	5th	172.28 ± 10.95	166.42 ± 13.45	156.00 ± 14.95	154.00 ± 14.95			

Values are mean ± SE. CON: control+sedentary; EX; control+exercise; GI: ginger; GI-EX: ginger+exercise. $^{**}p < .01$.

Table 3. The changes of insulin concentration

		CON	EX	GI	GI-EX	source	*F*	*p*
Insulin (ng/ml)	1st	2.85 ± 0.66	2.93 ± 0.86	2.92 ± 0.91	3.18 ± 0.55			
	2nd	3.09 ± 0.48	2.26 ± 0.74	2.29 ± 0.61	2.10 ± 0.49	time	5.060	.001**
	3th	3.37 ± 0.74	2.18 ± 0.41	2.45 ± 0.46	2.96 ± 0.84	group	2.056	.000**
	4th	3.29 ± 0.62	2.67 ± 0.49	2.51 ± 0.79	2.96 ± 0.67	time vs group	0.702	.179
	5th	3.46 ± 0.36	2.16 ± 0.58	1.56 ± 0.18	2.07 ± 0.58			

Values are mean ± SE. CON; control+sedentary, EX; control+exercise, GI; ginger, GI-EX; ginger+exercise. $^{**}p < .01$.

Table 4. The changes of HOMA-IR

		CON	EX	GI	GI-EX	source	*F*	*p*
HOMA-IR index	1st	4.99 ± 1.26	5.11 ± 1.48	5.17 ± 1.78	5.59 ± 1.24			
	2nd	5.69 ± 1.00	4.09 ± 1.16	4.22 ± 1.25	3.91 ± 1.05	time	6.486	.000**
	3th	5.27 ± 0.85	3.21 ± 0.68	3.80 ± 1.31	4.07 ± 1.30	group	3.862	.000**
	4th	5.43 ± 1.06	4.03 ± 0.70	4.19 ± 1.56	4.46 ± 1.14	time vs group	2.214	.017*
	5th	5.90 ± 0.78	3.35 ± 0.78	2.45 ± 0.17	3.18 ± 0.57			

Values are mean ± SE. CON; control+sedentary, EX; control+exercise, GI; ginger, GI-EX; ginger+exercise. $^{*}p < .05$, $^{**}p < .01$.

significant difference was found between periods × groups <Table. 3>.

HOMA-IR change was shown to significantly decrease in the EX, GI, and GI-EX groups ($p < .01$), and in the GI-EX group between the groups ($p < .01$), and in the GI-EX group for 2nd, 3rd and 5th analysis between periods × groups ($p < .05$) <Table. 4>.

Change in the antioxidant capacity of the skeletal muscle

SOD activity change in the gastroenemius was shown to increase in the GI-EX group, but no significant difference was found in the CON, EX, and GI groups. TBARS amount was shown to decrease in the EX and GI groups, but a significant difference was found. <Table. 5>

Change in the apoptosis of the skeletal muscle

No significant difference in the apoptosis change of the gastroenemius was found. However, anti-apoptosis factors such as Bcl-2 and Bcl-xl were shown to increase in the GI and GI-EX groups. In addition, p53 and caspase-3 were shown to decrease in the GI-EX group. <Fig. 2~5>.

Table 5. The changes of gastrocnemius SOD, TBARS in each group

	CON	EX	GI	GI-EX
SOD(U/mL)	18.69 ± 1.40	15.70 ± 3.43	14.49 ± 3.19	18.98 ± 2.22
TBARS(μM)	11.46 ± 1.29	8.79 ± 1.91	8.77 ± 1.91	11.24 ± 1.25

Values are mean ± SE.

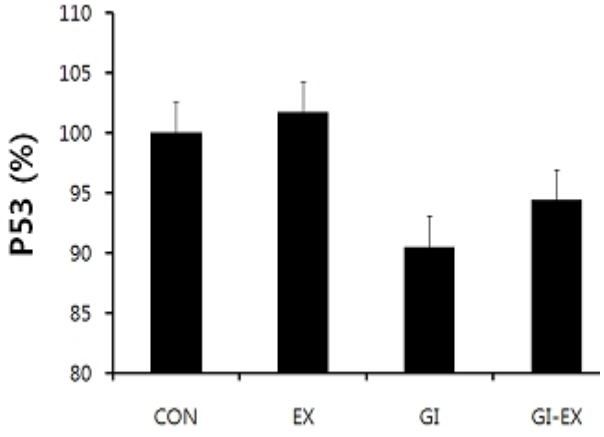

Fig 2. Changes of gastrocnemius p53 in each group. Values are mean ± SE. CON; control+sedentary, EX; control+exercise, GI; ginger, GI-EX; ginger+exercise.

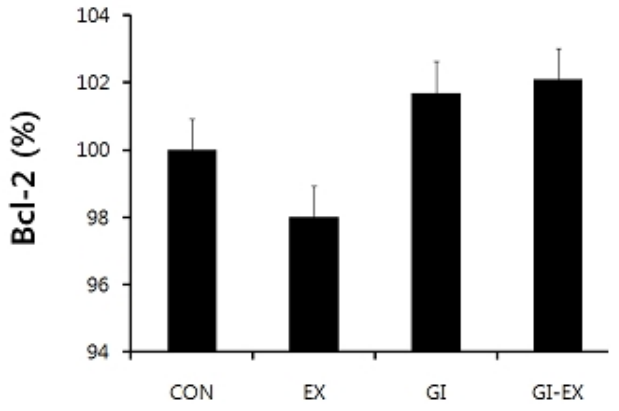

Fig 3. Changes of gastrocnemius Bcl-2 in each group. Values are mean ± SE. CON; control+sedentary, EX; control+exercise, GI; ginger, GI-EX; ginger+exercise.

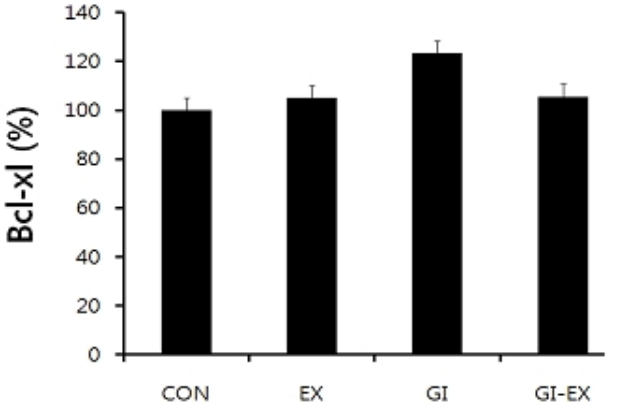

Fig 4. Changes of gastrocnemius Bcl-xl in each group. Values are mean ± SE. CON; control+sedentary, EX; control+exercise, GI; ginger, GI-EX; ginger+exercise.

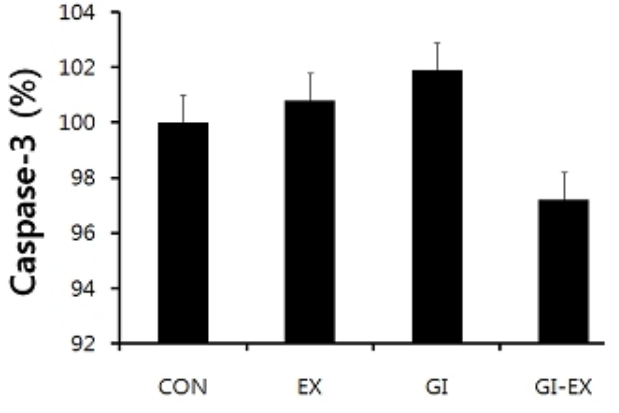

Fig 5. Changes of gastrocnemius caspase-3 in each group. Values are mean ± SE. CON; control+sedentary, EX; control+exercise, GI; ginger, GI-EX; ginger+exercise.

DISCUSSION

Ginger contains an approximately 1-2% of volatile oil and 5-8% of resinous material, starch, and mucus. Among the ingredients, volatile oils such as monoterpenes, sesquiterpenes, sesquiterpenes alcohol zingiberol, gingerol, and shagoals have been reported to be pharmaceutical activity mediators [23]. In addition, studies on the effect of ginger on anti-hyperglycemia, anti-oxidation, and anti-apoptosis have been conducted. In this study, the effect of the combinational treatment of ginger extract and swimming on insulin resistance, and the antioxidant capacity and anti-apoptosis of the skeletal muscle was investigated in hyperglycemic rats [19,24,25]. York *et al*. [26] reported that when the mixed extract of ginger, rheum, astragalus, salvia, and curcumin was administered to rats, the body fat decreased. Zingerone, which is a spicy ingredient of ginger, increased norepinephrine, resulting in degrading adipose cells and inhibiting fat storage, and thereby the reduction of weight and body fat [27,28]. In this study, a significant difference in weight was found but the weight was shown to decrease in the EX and GI-EX groups. The weight reduction is likely to be attributable to the spicy ingredient of ginger that affects energy consumption during exercise. In addition, the weight reduction in this study was likely to reduce body fat by causing the degradation of adipose cells.

Dietary therapy and exercise played an important role in blood glucose management [29]. In this study, the blood glucose was shown to significantly decrease in the GI and GI-EX groups. Ginger extract reduced glucose, insulin, and lipid concentrations [30]. Ginger treatment reduced blood glucose level by producing prostaglandins production, and that aerobic exercise had a positive impact on diabetic patients and blood glucose level as exercises caused physical stress and required glucose homeostasis and energy [31,32]. Thus, the results of this study were consistent with those of the previous studies.

Ingredients of ginger reduced PPAR-ɣ activity, which produces adiponectin, resulting in regulating glucose and increasing regulation and insulin sensitivity [33]. In addition, exercise reduced the reduction of TNF-a and adiponectin, resulting in increasing insulin sensitivity [34]. In this study, insulin concentration was shown to significantly decrease in the GI and GI-EX groups between periods, and in the GI-EX between groups. HOMA-IR was shown to significantly decrease in the EX, GI, and GI-EX groups between periods, and in the GI-EX group between groups, and in the GI-EX for 2nd, 3rd and 5th analysis between periods × groups. This result was consistent with those of previous studies, that ginger extract intake enhanced insulin secretion function [16],

and that exercise phosphorylated tyrosine of ObR/JAK2 and insulin receptors, leading to increase in leptin and insulin secretion increase. The combinational treatment of ginger extract and exercise is likely to reduce insulin resistance.

Hyperglycemia produces mtROS by increasing SIRT-1 (sirtuin-1) regulation [35]. For ROS reduction, ginger has been reported to remove hydroxy radical as it has antioxidation activity and to increase antioxidant enzymes in the liver [36,37]. In addition, exercise has been reported to reduce lipid peroxide by reducing mitochondrial markers in the skeletal muscle and lipids in the muscle in diabetic mouse [38]. In this study, SOD activity and TBARS concentration were shown to increase in the CON and GI-EX groups. Monounsaturated fat diet and regular exercise with an appropriate intensity increased not only SOD and GPx but also lipid peroxide in the skeletal muscle [39]. The mechanism that ginger intake increases antioxidant enzyme activity was unclear [40]. In this study, increase in antioxidant enzyme activity and no reduction of lipid peroxide were likely to be attributable to the fact that ROS production due to hyperglycemia increased TBARS and, to remove TBARS, antioxidation was activated, leading to increase in SOD and TBARS. A further study on the physiological activity of antioxidant enzymes of ginger and the combinational treatment with exercise is required.

Peterson *et al*. [41] reported that no significant difference in apoptosis was found in the gastrocnemius and the soleus muscle in diabetic rats for exercise, whereas a significant difference was shown in the cardiac muscle, and explained that that result was likely to be attributable to the significant influence of mitochondrial apoptosis to the heart. In addition, long-term exercise has been reported to reduce the apoptosis of the plantaris muscle [41,42]. Medicinal herbs have an ability of self-protection against apoptosis [43]. 6-shogaol reduced PARP (poly ADP-ribose polymerase) activity, resulting in reducing apoptosis, and explained that 6-gingerol, a spicy ingredient of ginger, activated ROS, resulting in reducing the expression of caspase-3,8,9 and COX-2 [44,45]. In this study, no significant difference in apoptosis was found. However, pro-apoptotic factor, p53 was shown to decrease in the GI and GI-EX groups, and the final apoptotic factor, caspase-3 was shown to decrease due to an increase in anti-apoptotic factors such as Bcl-2 and Bcl-xl. Antioxidant capacity increase, mitochondrial synthesis increase, and apoptosis decrease by the treatment of ginger extract and exercise are likely to be attributable to an increase in Bcl-2 and Bcl-xl due to the combinatial treatment of ginger extract and exercise, and eventually decrease in caspase-3, the final apoptotic factor.

CONCLUSION

This study was conducted to investigate the effect of swimming exercise and ginger extract intake on the antioxidant capacity and anti-apoptosis of the skeletal muscle in hyperglycemic rats. As a result, blood glucose, insulin, and HOMA-IR were shown to decrease in the EX, GI, and GI-EX groups. For antioxidant capacity change, no significant difference in SOD activity and TBARS amount due to ginger extract intake and exercise was found. For apoptosis mechanism, no significant difference in p53, caspase-3, Bcl-2 and Bcl-xl was found among the groups. In conclusion, the combinational treatment of ginger extract intake and exercise was effective in the improvement of insulin resistance in hyperglycemic rats. A further study on the effect of the combinational treatment of ginger extract intake and exercise on antioxidant capacity and apoptosis is required.

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