# *Panax Ginseng* Extract Ameliorates Disturbed Lipid Metabolism and Associated Thyroid Hormones in Sera of Alloxan-Induced Diabetic Rats

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**Abstract:** Diabetes mellitus is known to impair many physiological functions. Some reports claim that medicinal plants can reduce these alterations caused by Diabetes mellitus. The aim of this study was to investigate the effect of *Panax ginseng* extract (PGE), which is one of the most popular herbal remedies, on lipid profile and associated thyroid hormones in alloxan-induced diabetes in adult male albino rats. Animals were divided as follows: Control group (n=18), received 2ml of normal physiological saline solution (0.9% NaCl) for twenty one consecutive days. Alloxan monohydrate (ALX) group, (n=18); overnight fasted animals were made diabetic by a single subcutaneous (s.c.) injection of ALX (120mg/kg b.wt.) freshly prepared in 0.9% NaCl. *Panax ginseng* extract (PGE) group (n=18), animals were received a daily oral administration of (100mg/kg b.wt.) for 21 consecutive days. ALX & PGE group (n=18), animals were made diabetic by a single s.c. injection of ALX as shown in the 2nd group followed after one hour with oral administration of PGE as mentioned in the 3rd group, administration of PGE continued for 21consecutive days. All treated groups were decapitated at 7th, 14th and 21st days of treatment. Total lipids (TL), total triglycerides (TG), total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), triiodothyronine ($T_3$), tetraiodothyronine (thyroxine,$T_4$) and thyroid stimulating hormone (TSH) were assessed in blood sera of all treated groups. ALX-treated rats group revealed a significant elevation in TL, TG, TC and LDL-C, while indicating significant decreases in HDL-C, $T_3$, $T_4$ and TSH levels at all time intervals of the experiment. PGE administration to ALX-induced diabetic rats reversed the observed changes in the previously mentioned parameters as compared to ALX- treated group. Results of the present study indicate the ability of PGE to ameliorate the disturbed lipid metabolism and the involvement of thyroid hormones in counteracting ALX-induced diabetes in adult male albino rats.

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## 1. Introduction

Diabetes affects about 150 million people worldwide and it is expected to be doubled in the next 20 years **(Zimmet *et al.*, 2001)**. Type I diabetes is caused by the autoimmune destruction of pancreatic β-cells, and affects about 10% of patients with diabetes. Experimental induction of diabetes by alloxan (ALX) or streptozotocin (STZ) is a commonly used model with several correlations with insulin dependent diabetes mellitus in man **(Rerup, 1970)**. Diabetes mellitus is often associated with hyperlipidemia **(Kutty, 1994)**, the severity of which is dependent on the severity of the disturbances in carbohydrate metabolism and the degree of its control **(Betteridge, 1989)**.

Thyroid hormone is a key metabolic regulator coordinating short-term and long-term energy needs **(Oetting and Yen, 2007)**. Significant metabolic changes were observed with variations in thyroid status in humans **(Klein and Danzi, 2007).** Both diabetes mellitus and thyroid disorders are common diseases. According to epidemiologic studies the prevalence of specific thyroid disorders in diabetic subjects is two times higher **(Reismann and Somogyi, 2011)** than in normal subjects. Thyroid hormones play an important role in regulating energy balance, metabolism of glucose, and lipids **(Chubb *et al.*, 2005)**.

Herbs have been used for centuries to treat illness and improve health and still account for about 80% of medical treatment in the developing world with approximately one third of drugs being derived from plant sources **(Choi, 2008 and Kim *et al.*, 2008)**. *Panax ginseng* C. A. Meyer (Araliaceae) is one of the most widely used medicinal plants, particularly in traditional oriental medicine, for the treatment of various diseases. There are extensive reports that ginseng has many pharmacological effects on the central nervous system , endocrine, immune, and cardiovascular systems **(Kenarova *et al.*, 1990; Nah *et al.*, 1995; Wen *et al.*, 1996; Gillis, 1997 and Attele *et al.*, 1999)**.

This study, therefore, aimed to explore the effect of orally administered PGE in ameliorating disturbed lipid metabolism and associated thyroid hormones ($T_3$, $T_4$ and TSH) in sera after ALX-induced diabetes in albino rats.

## 2. Materials and Methods

### Chemicals

Alloxan was purchased from Sigma, U.S.A. as ALX monohydrate. PGE was obtained from Muggenburg, France. Gluco-test strips were purchased from Boehringer Mannheim Company, Germany. All other chemicals were of analytical grade.

### Experimental Animals

The experimental animals used in this study were of adult male albino rats (*Rattus norvegicus*) weighing 160-200g. They were housed under normal environmental conditions of temperature and humidity. Animals were kept under the normal light-dark rhythm while food and water were provided *ad libitum*.

### Experimental Protocol

Seventy-two rats were divided into four groups (18 rats each) as follows:

**1- Control Group:**

Animals of this group were injected subcutaneously (s.c.) with 0.5ml of physiological saline solution. One hour later, these animals were received an oral administration of 2ml saline solution which was repeated daily for 21 consecutive days.

**2-Alloxan Group (ALX):**

Animals were made diabetic by ALX monohydrate. Overnight-fasted animals were injected s.c. with a single dose of ALX (120mg/kg b. wt.) freshly prepared in 0.5ml of 0.9% NaCl. Glucosuria was evidenced by Gluco-test strips.

**3-Panax ginseng Extract Group (PGE):**

Animals of this group were received a daily oral administration of PGE (100mg/kg b. wt.) prepared in 2ml 0.9% NaCl for 21 consecutive days.

**4- Alloxan and Panax ginseng Extract Group (ALX & PGE):**

Overnight-fasted animals were injected s.c. with a single dose of ALX monohydrate (120mg/kg b. wt.). One hour later, these animals received an oral administration of PGE (100mg/kg b. wt.). Administration of PGE was repeated for 21consecutive days.

Overnight fasting animals were killed by fast decapitation (Six animals for each group) on the 7$^{th}$, 14$^{th}$ and 21$^{st}$ days of the experiment and the blood samples were collected immediately, stand for two hours and then centrifuged at 3000 r.p.m. for 15 minutes to separate serum.

### Determination of Lipid Parameters in Serum

Total lipids, TG, TC and HDL-C of serum were determined using kits from Biodiagnostic, Giza, Egypt. TL was measured according to the method described by **Zöllner and Kirsch (1962)**. TG was determined using the method of **Fossati and Prencipe (1982)**. TC was determined according to the method of **Allain *et al.* (1974)**. The assay of HDL-C was carried out by the method of **Lopez-Virella *et al.* (1977)** and LDL-C was calculated according to the method of **Farish and Fletcher (1983).**

### Hormonal Analysis

Serum levels of $T_3$, $T_4$ and TSH were assayed by the technique of enzyme linked immunosorbent assay (ELISA) using reagents by Dialab, Gesellschaft, Vienna, (cat. numbers Z01232, Z01208, and Z01237, respectively) as described by **Young *et al*. (1975).**

### Statistical Analysis

Results were expressed as mean ± standard error of mean (SEM). Percentage difference representing the percent of variation with respect to all groups was also calculated. Data for multiple variable comparisons were analyzed by one-way analysis of variance (ANOVA). For the comparison of significance between groups, Duncan's test **(Duncan, 1955)** was used according to Statistical Package for the Social Sciences (SPSS) version 10.

## 3. Results

The present study aimed to investigate the hypolipidemic effect of PGE against ALX- induced diabetes in rats after 7$^{th}$, 14$^{th}$ and 21$^{st}$ days of diabetes induction, and monitoring the changes in $T_3$, $T_4$ and TSH which play a role in lipid regulation and energy metabolism.

The data depicted in Table (1) revealed that ALX s.c. injection to overnight fasted albino rats resulted in a sharp significant increase in serum TL, TG, TC and LDL-C levels, if compared to control group, this increase persisted at the 7$^{th}$, 14$^{th}$ and 21$^{st}$ days of treatment. Whereas, HDL-C level exhibited a significant decrease ($p<0.001$) which was of highest value at the 21$^{st}$ day of diabetes induction with a percentage difference of -31.2% as compared to control group. Oral administration of PGE for 21 consecutive days revealed a significant decrease in TL, TG, TC and LDL-C levels, while showed an increase in HDL-C level at all time intervals of the experiment versus control group. Daily administration of PGE to ALX-induced diabetic rats for 21 consecutive days reduced significantly ($p<0.001$) the observed elevated lipid parameters level at all time intervals (except at 7$^{th}$ day for TL), if compared to ALX-treated rats group. At the 14$^{th}$ day of combined treatment, PGE decreased LDL-C level of sera of ALX–treated rats below control values with a percentage difference of -10.4% as compared to

control group. Moreover, PGE oral administration to ALX-treated rats enhanced the HDL-C level and exhibited a significant increase ($p<0.001$) at all days of the experiment as compared to both control and ALX- treated groups. The observed increase in HDL-C level indicated the ameliorative effect of daily administration PGE on diabetic rats.

**Table (1): Effect of ALX-induced diabetes (120mg/kg b.wt., s.c.) and/or daily oral administration of PGE (100mg/kg b.wt.) for 7, 14 and 21 consecutive days on serum lipid profile of adult male albino rats.**

| Groups / Serum | Experimental Days | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 7th | | | | 14th | | | | 21st | | | |
| | Control | ALX | PGE | ALX &PGE | Control | ALX | PGE | ALX& PGE | Control | ALX | PGE | ALX& PGE |
| TL (g/l) | 5.90±0.14 | 6.47±0.11 (9.7) a | 5.45±0.10 (-7.6) a | 6.1±0.23 (3.4) c | 5.95±0.14 | 7.06±0.11 (18.7) a** | 5.53±0.13 (-7.1) | 5.83±0.13 (-2.0) b** | 5.48±0.08 | 8.90±0.25 (62.4) a** | 5.65±0.14 (3.1) | 5.97±0.12 (8.9) ab** |
| TG (mg/dl) | 86.5±3.0 | 138.3±2.8 (59.9) a** | 67.5±1.3 (-22.0) a** | 112.6±2.2 (30.2) a**b**c** | 84.5±4.1 | 145.4±3.3 (72.1) a** | 62.3±2.3 (-26.3) a** | 104.2±1.1 (23.3) a**b**c** | 84.0±1.9 | 158.8±4.2 (89.0) a** | 64.1±1.2 (-23.7) a** | 100.8±0.8 (20.0) a**b**c** |
| TC (mg/dl) | 182.9±7.5 | 324.5±3.5 (77.4) a** | 139.0±1.9 (-24.0) a** | 262.3±1.9 (43.4) a**b**c** | 185.4±7.1 | 320.8±2.6 (73.0) a** | 133.8±1.8 (-27.8) a** | 216.9±1.9 (17.0) a**b**c** | 185.5±3.1 | 328.3±3.4 (77.0) a** | 133.6±1.4 (-28.0) a** | 210.6±1.4 (13.5) a**b**c** |
| HDL-C (mg/dl) | 86.1±1.2 | 72.7±0.4 (-15.6) a** | 105.3±2.5 (22.3) a** | 102.4±1.5 (18.9) a**b** | 84.9±0.8 | 66.8±1.0 (-21.3) a** | 111.1±1.6 (30.9) a** | 121.0±3.9 (42.5) a**b**c | 86.0±1.2 | 59.2±0.5 (-31.2) a** | 107.6±3.2 (25.1) a** | 99.2±1.5 (15.3) a**b**c |
| LDL-C (mg/dl) | 78.2±8.6 | 239.5±16.8 (206.3) a** | 22.4±4.7 (-71.4) a** | 137.4±2.1 (75.7) a**b**c** | 82.6±6.3 | 225.6±3.7 (173.1) a** | 11.1±0.6 (-86.6) a** | 74.0±3.9 (-10.4) ab**c** | 82.1±3.9 | 218.1±18.9 (165.7) a** | 14.7±3.6 (-82.1) a** | 92.0±4.0 (12.1) a*b**c** |

Data are represented as mean ± SE (n=6 in each group)
a: Significant change at $p<0.05$ with respect to control group.
b: Significant change at $p<0.05$ with respect to ALX group.
c: Significant change at $p<0.05$ with respect to PGE group.
* Significant change at $p<0.01$
** Highly Significant change at $p<0.001$.
( ) % difference with respect to control value.

**Table (2): Effect of ALX-induced diabetes (120mg/kg b.wt., s.c.) and/or daily oral administration of PGE (100mg/kg b.wt.) for 7, 14 and 21 consecutive days on serum TSH, $T_3$ and $T_4$ levels of adult male albino rats.**

| Groups / Serum | Experimental Days | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 7th | | | | 14th | | | | 21st | | | |
| | Control | ALX | PGE | ALX &PGE | Control | ALX | PGE | ALX& PGE | Control | ALX | PGE | ALX& PGE |
| TSH (µIU/dl) | 5.8±0.12 | 4.7±0.11 (-19.0) a** | 5.4±0.10 (-6.9) | 5.4±0.13 (-6.9) b** | 6.1±0.13 | 4.3±0.11 (-29.5) a** | 6.2±0.11 (1.6) | 5.3±0.13 (-13.1) a*b**c** | 6.2±0.14 | 4.0±0.15 (-35.5) a** | 6.5±0.14 (4.8) | 5.2±0.14 (-16.1) a*b**c** |
| T3 (ng/ml) | 0.58±0.03 | 0.36±0.01 (-37.9) a** | 0.55±0.01 (-5.2) | 0.48±0.02 (-17.2) a**b**c | 0.68±0.02 | 0.21±0.02 (-69.1) a** | 0.58±0.01 (-14.7) a** | 0.45±0.01 (-33.8) a**b**c* | 0.64±0.01 | 0.22±0.01 (-65.6) a** | 0.60±0.02 (-6.25) | 0.57±0.01 (-10.9) a**b** |
| T4 (µg/dl) | 9.8±0.22 | 5.3±0.20 (-45.9) a** | 9.2±0.18 (-6.1) a* | 5.0±0.19 (-49.0) a**c** | 10.1±0.19 | 3.9±0.24 (-61.4) a** | 10.0±0.22 (-1.0) | 4.6±0.20 (-54.5) a**b**c** | 9.6±0.23 | 4.3±0.19 (-55.2) a** | 9.2±0.21 (-4.2) | 8.0±0.22 (-16.7) a*b**c |

Data are represented as mean ± SE (n=6 in each group)
a: Significant change at $p<0.05$ with respect to control group.
b: Significant change at $p<0.05$ with respect to ALX group.
c: Significant change at $p<0.05$ with respect to PGE group.
* Significant change at $p<0.01$
** Highly Significant change at $p<0.001$.
( ) % difference with respect to control value.

The data illustrated in Table (2) showed that TSH, $T_3$ and $T_4$ levels were reduced significantly at all days of the experiment as compared to control group which might be due to hyperglycemic extremes resulting from ALX-induced diabetes. Although, PGE administration exhibited non significant decreases in $T_3$ and $T_4$, a significant decline, for both hormones, was noticed at the $14^{th}$ and $7^{th}$ days, respectively, if compared to control group. Combined administration of PGE to ALX-diabetic rats enhanced TSH, $T_3$ and $T_4$ with a significant sign at $p<0.001$ showing a gradual increase towards control level, at the $7^{th}$ ,$14^{th}$ and $21^{st}$ days of treatment (except at $7^{th}$ day for $T_4$) if compared to ALX- treated rats group.

**4. Discussion**

Ginseng is widely used in oriental societies as one of the most valuable medicines. Active constituents with curable features found in most of ginseng species include ginsenosides, polysaccharides, peptides, polyacetylenic alcohols, and fatty acids **(Choi, 2008**). Ginseng-specific saponins (ginsenosides) were considered as the major bioactive compounds for the metabolic activities of ginseng **(Yin *et al.,* 2008)**. Ginsenosides, have been studied as major pharmacological components and were known to have also mitogenic activities with a variety of effects such as anti-diabetic, anti-cancer, anti-inflammatory, antihyperlipidemic and anti-atherosclerosis activities **(Choi, 2008; Lee and Jeong, 2008; Min *et al.,* 2008; Park and Cho, 2008 and Park *et al.,* 2008**).

Studies were inconsistent and contradictory in that some suggested that ginseng exhibited hypolipidemic action in experimental animal systems, such as hypercholesterolemic rabbits, high-cholesterol diet-fed rats, and patients with hyperlipidemia **(Yamamoto** *et al.,* **1983; Cui** *et al.,* **1998 and Inoue** *et al.,* **1999)**, whereas in other reports ginseng administration failed to exert any beneficial effects on hypercholesterolemia in rabbits **(Ismail** *et al.,* **1999)**.

Results obtained from the present study indicate that ALX injection induced a sharp increase in TL, TG, TC and LDL-C serum levels of albino rats accompanied with a significant increase in HDL-C content in sera of ALX- treated rats group. In diabetes, there is a decreased conversion of glucose to fatty acids level in the plasma, also increased level of glycerol and ketones **(Taylor and Agius, 1988)**. Experimentally diabetic rats are characterized by elevated plasma TG and TC levels **(Wasan *et al.,* 1998)**.

PGE administration for 21 consecutive days decreased TL, TG, TC and LDL-C levels while increased HDL-C level in sera of PGE-treated rats group, with respect to control group. Similar results were obtained in sera of combined ALX & PGE treated group with respect to ALX-treated rats group. It has been reported that non saponin fractions of Korean red ginseng were capable of inhibiting epinephrine-induced lipolysis and of stimulating insulin-mediated lipogenesis from glucose in rat adipocytes **(Takako *et al.,* 1990)** Acidic polysaccharides from ginseng root were found to inhibit toxohormone L-induced lipolysis **(Takako *et al.,* 1990)**, modulate pancreatic lipase activity and caused a reduction in plasma TG levels after oral administration of corn oil emulsion to rats, implying the involvement of pancreatic lipase in the reduction of lipolysis **(Joo *et al.,* 1999).**

Ginseng was found to inhibit markedly lipid peroxidation in testes of Swiss albino mice after radiation treatment **Kumar *et al.,* (2003)**. Moreover, **Kim and Park (2003)** suggested that the hypolipidemic effect of PGE was associated with decreased TC, TG, LDL-C, malonaldehyde levels and increased HDL-C level, increased superoxide dismutase, catalase activities and decreased malonaldehyde level indicating the antioxidant potential of PGE which might induce hypolipidemic effect as one of its action mechanism.

American ginseng and Chinese red ginseng administration through diet, led to reduction of TC and TG levels in avian liver and serum **(Qureshi *et al.,* 1983)**. The authors attributed the decrease in TC and LDL–C to the suppression of β-hydroxy-β-methylglutaryl-CoA reductase and cholesterol 7 α-hydroxylase activities. In rats and patients fed on high-cholesterol diet to generate hyperlipidemia, administration of red ginseng powder was found to reduce plasma TC, TG, free fatty acids, platelet adhesiveness, and increased HDL-C significantly **(Yamamoto *et al.,* 1983)**.

Korean red ginseng extract(KRGE) was found to reduce the serum levels of TC, LDL-C, TG and atherogenic indices in mice fed long-term on a high-fat diet **(Song *et al.,* 2012)**, while levels of leptin, adiponectin and insulin, which regulate glucose and lipid metabolism, were impaired profoundly. However, the authors found that KRGE treatment brought these levels back to normal. KRGE was found to down-regulate genes associated with lipid metabolism or cholesterol metabolism which were up-regulated by high-fat diet. The authors further suggested that KRGE regulated the expression of genes associated with abnormal physiology via fed high-fat diet as it modulates leptin, insulin and adiponectin, which carry out critical functions in energy and lipid metabolism, thus preventing obesity.

Results obtained from the present work indicate that ALX injection induced a significant decrease in TSH, $T_3$ levels and the decrease was very sharp in $T_4$ level in sera of ALX-treated group as compared to

control group. PGE continuous administration, for 21 days, to diabetic rats ameliorated the decrease in thyroid hormones level, especially that of $T_4$, if compared to ALX-treated group.

Ginseng injection was found to have a good effect on patients with chronic heart failure and regulatory effect on thyroid hormones (**Dai *et al.*, 1999**). Moreover, treatment with *Panax ginseng* before, during or after acrylamide treatment reduced or partially antagonized increased serum serotonin, corticosterone, $T_3$, $T_4$, TSH, estradiol, progesterone and plasma adrenaline induced by acrylamide towards the normal values of controls (**Mannaa *et al.*, 2006**). The authors concluded that PGE exhibited a protective action against acrylamide toxicity and pointed that treatment with *Panax ginseng* extract before or at the same time as acrylamide treatment was more effective than when administered after acrylamide treatment.

The thyroid hormone $T_3$ exhibits an extensive range of physiological functions, which were related to the regulation of thermogenesis, metabolism, systemic vascular resistance, heart rate, renal sodium reabsorption and blood volume **(Crunkhorn and Patti, 2008)**. Cellular membranes are relatively impermeable to thyroid hormone and thus membrane transporters are necessary for access to the intracellular environment **(Heuer and Visser, 2009).** Once inside the cells, thyroid hormone diffuses toward the nucleus and eventually binds to its receptors, high affinity ligand-dependent transcription factors that modify gene expression (**Cheng *et al.*, 2010**). Regulation of circulating thyroid hormone and $T_3$ availability at the local tissue level is a critical step in metabolic control. $T_3$ exerts its functions by binding to the thyroid hormone receptors, TRα1 and TRβ1 (receptor nomenclature follows **Alexander** *et al.*, **2009)**. Binding of $T_3$ to TR de-represses TRE-dependent genes and induces the expression of various target genes. Nutritional status feedback at the level of the hypothalamus influences the thyroid releasing hormone set-point and the resulting circulating thyroid hormone levels. Bile acids directly stimulate deiodinase 2 ($D_2$) that converts the prohormone $T_4$ to $T_3$ or it can be inactivated to form reverse $T_3$ via the type 3 deiodinase **(Bianco, 2011)**.

Thyroid hormones were found to regulate the expression of enzymes involved in all steps of lipid metabolism leading to the development of qualitative and quantitative changes of lipids in thyroid disease **(Peppa *et al.*, 2011)**. Thyroid hormones affect lipoprotein lipase activity and thus, the hydrolysis of TG into very-low density lipoprotein (VLDL) and chylomicrons into fatty acids and glycerol (**Zhu and Cheng, 2010)**. Thyroid receptors seem to mediate the effects of thyroid hormones on lipid metabolism, and more specifically alpha 1 receptors control the lipogenesis in white adipose tissue and $\beta$ receptors regulate the activity of lipogenic and lipolytic enzymes in the liver **(Zhu and Cheng, 2010)**.

Peroxisome proliferator-activated receptor **α** (PPAR**α**) which is a member of the steroid/thyroid hormone receptor super family was found to regulate the expression of a number of genes critical for lipid and lipoprotein metabolism. PPAR**α** was also found to initiate TG-lowering effects through transcriptional activation of peroxisomal, microsomal and mitochondrial fatty acid-metabolizing enzymes as well as lipoprotein lipase and apolipoprotein CIII **(Auwerx *et al.*, 1996)**. PPAR**α** was known to increase the circulating amounts of HDL-C levels through induction of apolipoprotein AI and AII gene expressions **(Staels and Auwerx, 1998).** The absence of PPAR**α** results in abnormalities in TG and TC metabolism because of reduced lipoprotein and fatty acid metabolism **(Costet *et al.*, 1998)**.

There is evidence to suggest that ginseng can interact with nuclear receptors including PPAR**α**. **Huang (1999)** reported that regulation of lipid metabolism by PPAR**α** would seem to be a logical target if ginseng and its pharmacologically active steroidal saponins exert their effects on serum lipids as a result of interactions with nuclear receptors. This indicate that the effects of ginseng on serum lipid profiles may be mediated by changes in the expression of PPAR**α** target genes thus inhibiting PPAR**α** function which may have therapeutic implications.

Alloxan induces damage and death of pancreatic islet β-cells in experimental models, thus causing type I diabetes. Alloxan causes permanent diabetes not only in rabbit or rat, but also in several species **(Daniel and Jeffrey, 1981)**. One of the main processes involved in the insulin-producing β-cell death is apoptosis, which leads to insulin deficiency. To treat or even to prevent the onset of type I diabetes, this may imply an anti-apoptotic pro-survival therapy of β-cells **(Verga Falzacappa *et al.*, 2011)**. The authors proposed that $T_3$ treatment to STZ-induced diabetic rats, prevented STZ-induced cells damage and islets deterioration (clumped chromatin, disorganized insulin-containing granules, altered mitochondria, endoplasmic reticulum and vacuoles morphology).

In addition, **Luo and Luo (2006)** indicated that ginseng was found to induce expression of anti-apoptotic factor Bcl-2 while suppress expression of pro-apoptotic factor caspase-9. The antioxidant activity of ginsenosides was involved in the anti-apoptosis activity as production of free radicals, such

as nitric oxide (NO) and reactive oxygen species was reduced by ginsenoside **(Kim and Kim, 2007)**.

Thyroid hormones are widely known for their ability to influence various cellular processes such as mitogenesis and differentiation which are both considered good candidate targets for counteracting the insurgence of diabetes **(Oetting and Yen, 2007)**. Moreover, **Misiti *et al.* (2005)** showed that $T_3$ acts as a mitogenic, protective and pro-survival factor in pancreatic β-cells undergoing apoptosis.

**Verga Falzacappa *et al.* (2010)** analyzed the ability of β-cells to counteract apoptosis induced by STZ using TUNEL assay and demonstrated that treatment of primary cultures of rat pancreatic islets with $T_3$ resulted in augmented β-cell vitality with an increase in their functional properties. Moreover, the authors proposed that thyroid hormone $T_3$ might be a suitable factor to optimize and stimulate recovery and subsequent function of islets, indicating the important role of thyroid hormone in biophysiological function of pancreatic islets.

It could be concluded from the present study that PGE oral administration ameliorates the increased TL, TG, TC and LDL-C levels in sera of ALX-induced diabetic rats and increased the beneficial HDL-C level, T3, $T_4$ and TSH contents. This could be attributed to ginseng-specific ginsenosides, saponins, which were considered as the major bioactive compounds for the metabolic activities of ginseng.

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