Cibtech Journal of Zoology ISSN: 2319–3883 (Online)
An Open Access, Online International Journal Available at http://www.cibtech.org/cjz.htm
2017 Vol. 6 (1) January-April, pp.1-8/Khaksar and Karami
Research Article

THE EFFECT OF PRESCRIPTION OF *PANAX GINSENG* ALCOHOLIC EXTRACT ON CEREBRAL AND CEREBELLAR HISTOMORPHOMETRIC CHANGES IN 20-DAY RAT FETUSES OF DIABETIC MOTHERS

***Zabihollah Khaksar and Azam Karami**
Department of Basic Sciences, School of Veterinary Medicine, Shiraz University, Shiraz, Iran
**Author for Correspondence*

ABSTRACT
Despite enormous progresses in controlling diabetes complications in pregnant women, the risk of birth abnormalities and also defect in the nervous system is still significantly higher than the healthy population. And since diabetes control can considerably help to prevent bad complications in fetus, and due to the issue that chemical medications have also different complications on fetus, this study is aimed to evaluate the effect of Panax ginseng alcoholic extract on histomorphometric changes of the cerebrum and the cerebellum in 20-day-old rat fetuses born to mothers with diabetes in order that herbal medicines with minimal side effects than chemical medications to be found and be recommended to diabetic mothers. 32 adult female Sprague-Dawley rats weighing about 200-250 grams were prepared. After 10 days, the rats were randomly divided into four groups of 8 that include: 1- non-diabetic control (the rats were not diabetic during the research and did not receive Panax ginseng extract), 2- ginseng control (the rats in this group received their daily Panax ginseng extract orally at dose of 400 mg/kg body weight), 3- diabetic control (included the rats that became diabetic during the experiment but did not get the Panax ginseng extract), 4- treated group with ginseng (the rats in this group became diabetic during the experiment and got 400 mg/kg body weight of their daily Panax ginseng extract orally during the pregnancy). The mothers were anesthetized on the 20th day of pregnancy and their fetuses were removed for study of cerebral and the cerebellar tissues. By passing the histological steps and preparation of the slides, the cerebrum and the cerebellum were compared and studied in terms of thicknesses of white matter and gray matter, ratios of white matter and gray matter, the count of neuroglial cells per unit area in the white matter and the gray matter. The results of this research showed that gray matter thickness, gray matter cell count, white matter cell count, and gray matter to white matter ratio in the cerebrum of 20-day-old rat fetuses decreased significantly in the diabetic group compared to the non-diabetic group. Gray matter thickness, gray matter cell count, white matter cell count, and gray matter to white matter ratio in the cerebellum of 20-day-old rat fetuses also decreased significantly in the diabetic control group compared to the non-diabetic control group. The results showed that increase in the number of nerve cells and the nerve layer thickness in the treated group with ginseng extract was observed compared to the diabetic control group. Based on the results it becomes clear that consumption of Panax ginseng extract is effective in improvement of the cerebrum and the cerebellum in 20-day-old rat fetuses born to mothers with diabetes and this extract can be helpful to improve the development of the cerebrum and the cerebellum in such animals.

Keywords: *Panax Ginseng, Histomorphometric, Cerebrum, Cerebellum, Fetus, Diabetes*

INTRODUCTION
Diabetes mellitus is one of the most common diseases of the body's endocrine system. The disease is due to the lack of cellular uptake of blood glucose resulting from decreased secretion of insulin or resistance of the body cells to insulin (Li *et al.,* 2004; Nakamura *et al.,* 2006). Diabetes mellitus has two types including insulin dependent diabetes (type 1) and non-insulin dependent diabetes (type 2). Gestational diabetes occurs in more than 8 percent of all pregnancies (Moore, 2004).
Despite enormous progresses in control of diabetes complications in the pregnant women and risk of birth abnormalities in newborns are still significantly more than healthy population. Laboratory studies have

also approved the harmful effects of diabetes on fetus (Lucas, 2001). Diabetes during pregnancy has been studied due to increased fetal complications such as macrosomia, congenital malformations, gestational injuries, preterm delivery, unexplained fetal death, and complications after birth (Nakamura *et al.,* 2006; Pampfer *et al.,* 1997).

The nervous system is one of the most important organs, which is damaged due to diabetes (Wyngaarden and Smite, 1982). Gestational diabetes in human occurs on the 24th week of pregnancy, but some cases of abnormal formation of the central nervous system and spinal cord had been observed in the fetus (Aberg *et al.,* 2002).

Thus, since pregnancies affected by diabetes are at high risk of unpleasant effects near the time of delivery, fetal malformations and development of type 2 diabetes in the future, treatment interventions are necessary (Gabbe *et al.,* 2004).

Now, original and effective treatment of diabetes is use of insulin and glucose-lowering chemical drugs. However, these medicines have numerous side effects. Therefore, achievement to compounds that with minimal side effects can reduce blood sugar during pregnancy and also have the least adverse complications on the fetus seems necessary. With regard to this issue that medicinal plants have fewer side effects than chemical medicines, researchers are searching for herbal compounds for treatment and/or prevention from the disease (Isah *et al.,* 2007).

Ginseng (Panax ginseng) root from Araliaceae family was used in this study. The roots of this plant contain a steroidal glycoside called ginsenoside. Ginsengin traditional medicine is used to treat diabetes and also used as a food supplement (Shishtar and Jovanovski, 2014).

Thus, based on the above as well as the adverse effects of maternal diabetes on fetal cerebral and cerebellar development, the current study is performed by this aim to assess and compare probable histomorphometric changes caused by prescription of Panax ginseng root extract on the cerebrum and the cerebellum of 20-day-old rat fetuses born to diabetic mothers.

MATERIALS AND METHODS

Methods

32 adult female Sprague-Dawley rats weighing approximately 200-250 g were prepared. After selection process, the rats were kept in new conditions and in standard cages for 10 days until necessary compliances were met. Two rats were kept in each cage. After 10 days, the rats were randomly divided into four groups of 8 each.

The first group: this is the group that the rats were not diabetic during the research and did not receive Panax ginseng extract (non-diabetic control group).

The second group: this is the group that the rats were not diabetic during the research but they received their daily Panax ginseng extract orally at dose of 400 mg/kg body weight during their pregnancy (ginseng control group) (Raya *et al.,* 2013).

The third group: these are the rats that became diabetic during the experiment but did not get the Panax ginseng extract (diabetic control group).

The fourth group: the rats in this group became diabetic during the experiment and got their daily 400 mg/kg body weight of the Panax ginseng extract orally during the pregnancy (treated group with ginseng) (Raya *et al.,* 2013).

Streptozotocin was used during the experiment for induction of diabetes. This medicine at dose of 50 mg/kg body weight was injected intraperitoneally (Fahimeh, 1999; Roghani *et al.,* 1999 Nikbakht and Ghaytasi, 2006).

Blood sugar test was performed prior to injection, 24 hours after injection to verify diabetes and 10 days after the injection for awareness from stabilization of diabetes. The blood samples were taken from the tail and through a small incision on superficial veins at extremity of the tail.

A glucose meter device called Accu-Chek (made in Germany) was used to measure blood glucose levels. Blood glucose higher than 250 mg/dl was considered as the criteria for diagnosis of diabetes (Jafari and Khaksar, 2012).

In order to prepare ginseng extract, ginseng (Panax ginseng) raw root was firstly obtained from valid centers, and then the roots were steamed at 100 ˚C for two hours. After this process, the roots were dried at 60 ˚C and the resultant material is called red ginseng (Lee and Yun, 2011). Red ginseng roots were powdered using electric mill. 1000 g of red ginseng root powder was soaked in 2 liters of 90% ethanol, kept in refrigerator for five days and the mixture was stirred together daily (Raya *et al.,* 2013; Diveband *et al.,* 2010). The amount needed of dried powder of red ginseng was dissolved dailyin water and the animals were fed from it by oral tubes.

After stabilization of diabetes (occurrence of increased levels of blood glucose and urine volume), female rats were placed at the right time in the cages of male rats to create fertility in females. On the 20th day of gestation two mother rats from every four studied groups were anesthetized and their embryos were removed by cesarean and formation and development processes of the central nervous system were studied histomorphometrically.

By separating the fetal central nervous system, at least five fetuses in various groups were studied for microscopic evaluation. Sampling was done form the cerebrum and the cerebellum associated with the brain stem of the fetuses for histomorphometric studies. The provided sections were stained with hematoxylin and eosin stain and Masson trichrome (green) stain. The cerebrum and the cerebellum were studied in terms of gray matter and white matter thicknesses, gray matter to white matter ratio, gray matter cell count, and white matter cell count per unit area (1 mm^2). Finally, the obtained information were analyzed using one-way ANOVA test and Duncan test and the significance level was considered at $p<0.05$.

RESULTS AND DISCUSSION

Results

The results of histomorphometric study of cerebral tissue in 20-day-old rat fetus revealed that gray matter thickness, gray matter cell count, white matter cell count as well as gray matter to white matter ratio in the diabetic control group had a significant reduction ($p<0.05$) compared to non-diabetic control and ginseng control groups, which reflects the negative effect of the mentioned factors in gray matter and white matter of cerebrum in 20-day-old rat fetuses with diabetic mothers. On the other hand improvement in gray matter thickness and white matter cell count of the cerebrum was observed in treated groups with ginseng, which none of them showed a significant difference and only an increase in gray matter cell count of cerebrum in the treated group with ginseng showed a significant difference compared with diabetic control group ($p<0.05$).

The results of histomorphometry study of cerebellar tissue in 20-day-old rat fetuses showed that gray matter thickness, gray matter cell count and white matter cell count in the diabetic control group had a significant reduction compared with the healthy control and ginseng control groups ($p<0.05$). Improvement in gray matter thickness, gray matter cell count and white matter cell count was revealed in the treated group with ginseng. However, it was not statistically significant compared to the diabetic control and the non-diabetic control groups (Table 1).

Discussion

The results of this study showed that gray matter thickness, gray matter cell count, white matter cell count, and gray matter to white matter ratio in the cerebrum of 20-day-old rat fetuses had significant decrease in the diabetic group compared to the non-diabetic control group ($p<0.05$). Gray matter thickness, gray matter cell count, and white matter cell count in the cerebellum of 20-day-old rat fetuses in the diabetic control group had a significant reduction compared to the non-diabetic control group ($p<0.05$).

In the past study on histomorphometric changes of cerebellum in 20-day-old rat fetuses with diabetic mothers have indicated that gray matter thickness, gray matter cell count, and gray matter to white matter ratio of the cerebellum in diabetic group compared with other groups in 18 and 20-day-old fetuses as well as white matter cell count of the cerebellum in 18-day-old fetuses were significantly lower (Rafati *et al.,* 2013). This is consistent with the results of the current study.

Table 1: The Results Related to Evaluation of Cerebral and Cerebellar Tissues of 20-Day-Old Rat Fetuses in Various Groups

Groups / Studied Factors	Non-Diabetic Control	Ginseng Control	Diabetic Control	Treated with Ginseng
Gray matter thickness of cerebrum (3m)	486.22 ± 37.31 a	483.81 ± 36.25 a	401.17 ± 34.19 b	447.83 ± 39.11 ab
White matter thickness of cerebrum (3m)	311.76 ± 28.43	313.26 ± 27.18	322.19 ± 30.17	316.45 ± 27.64
Gray matter cell count of cerebrum (n/mm^2)	25786.48 ± 917.64 a	25719.91 ± 894.28 a	22749.38 ± 716.43 b	24498.83 ± 738.22 a
White matter cell count of cerebrum (n/mm^2)	10917.65 ± 418.52 a	10947.12 ± 437.11 a	9856.41 ± 447.25 b	10584.63 ± 422.04 ab
Gray matter to white matter ratio in cerebrum	1.77 ± 0.07 a	1.75 ± 0.06 a	1.56 ± 0.06 b	1.64 ± 0.08 ab
Gray matter thickness of cerebellum (3m)	587.42 ± 41.65 a	581.14 ± 42.09 a	447.63 ± 39.12 b	501.84 ± 38.92 ab
White matter thickness of cerebellum (3m)	43.25 ± 4.35	44.08 ± 4.18	38.64 ± 3.91	40.29 ± 4.07
Gray matter cell count of cerebellum (n/mm^2)	26311.91 ± 1004.41 a	26279.42 ± 974.11 a	23857.39 ± 899.14 b	25714.32 ± 959.13 ab
White matter cell count of cerebellum (n/mm^2)	15401.62 ± 479.45 a	15419.51 ± 485.36 a	14389.57 ± 451.36 b	14875.66 ± 471.31 ab
Gray matter to white matter ratio in cerebellum	16.73 ± 1.31	16.68 ± 1.35	15.52 ± 1.29	16.03 ± 1.28

* According to Duncan's test, similar letters show lack of significant difference at $p<0.05$ among various groups

Studies have revealed that gestational diabetes mellitus is occurred in 8% of pregnancies (Moore, 2004). Laboratory studies have also approved the harmful effects of diabetes on the fetus. The fetus is influenced by hormonal and metabolic changes of the mother's body during pregnancy. These changes can have significant effects on the growth and development of various organs of the fetal body (Lucas, 2001). Studies have also stated that the nerve system is one of the most important body parts damaged by the disease (Wyngaarden and Smite, 1982). Diabetes by affecting on the brain causes neurophysiological changes and disruption in structure and function of the brain such as reduction in gray matter density (Musen *et al.,* 2006). Other studies have shown that type 1 diabetes causes disruption and disorder in the structure of the cerebellum or may cause hypoplasia or lack of neonatal cerebellar development (Bayreuther *et al.,* 2008, Hoveydaa *et al.,* 1999). Khaksar *et al.,* (2010) by examination the effect of maternal diabetes on histomorphometric changes of cerebellum in rat fetuses have shown that hyperglycemia that occurs in fetuses due to maternal diabetes causes reduction in cell count and gray matter thickness of the cerebellum. As the results of this research showed some irregularities in gray matter to white matter ratio of the cerebrum and the cerebellum occur in the diabetic control group. Gray matter thickness of the cerebrum and the cerebellum of 20-day-old rat fetuses in the diabetic control group showed a reduction compared to the non-diabetic control group, which reflects the negative effect of diabetes on thickness as well as on gray matter cell count and white matter cell count of the two organs. Studies have shown that the average volume of gray matter reduces in some areas of the brain due to diabetes. The reduction of average volume of white matter also occurs in other areas of the brain. So, the issue that gray matter and white matter thicknesses in diabetic groups should be simultaneously influenced in all areas of the brain is not possible. In some areas the gray matter thickness and in other areas the white matter thickness can be affected by diabetes (Northam *et al.,* 2009). So, the thickening of white matter occurred in the cerebrum and the cerebellum of 20-day-old rat fetuses as a result of diabetes in this study, suggesting that diabetes did not cause the decrease in white matter thickness in both mentioned areas of the fetuses. But the fact that diabetes has negative impacts on cerebrum and cerebellum tissues of the fetus is undeniable and is consistent with the results of previous researches.

Studies have found that fetuses and babies born to mothers with diabetes are faced with reduced cell count and gray matter thickness of cerebellum (Khaksar *et al.,* 2010). Cerebellar hypoplasia may also occur in fetuses and babies born to diabetic mothers (Gabbe *et al.,* 2004). Another research found the inhibitory effect of hyperglycemia on neuropeptide Y (NPY), a major neurotransmitter of fetal brain, synthesis (Singh *et al.,* 1997). It has stated that during fetal life in diabetic group increased blood glucose occurs due to high blood glucose of mother and enhancement in its transfer to the fetus through the placenta (Almeida *et al.,* 2002). This may cause neuropathy and neuronal loss in the fetus (Tehranipour and Khakzad, 2008). It is also possible that in this study, a decrease in the number of neurons in the cerebral and cerebellar gray areas occurred as a result of possible rise in blood glucose of the fetus. This is consistent with the results of other researches. Studies revealed that blood vessels of nerves are damaged due to diabetes, this causes damage to the nerve, resulting nervous cell death caused by ischemia. It is believed that hyperglycemia can aggravate ischemic injury (Wyngaarden and Smite, 1982). Studies have revealed that diabetes and diabetes-induced ischemia causes oxidative stress as a result of dysfunction in mitochondrial respiratory chain and itself causes overproduction of reactive oxygen which is considered as the main factor in pathogenesis of cell death (Iwasaki *et al.,* 2001). Studies have shown that free radicals due to their strong desire to catch up electrons, cause damage to other molecules such as fatty acids of biological membranes and their oxidation. As a result, fluidity, structure and function of membrane are compromised (Rice Ewans and Eurdon, 1994). Creation of oxidative stress in the diabetic groups in the current study may probably the cause for reduced number of neurons as well as thickening of the nervous layer in cerebrum and cerebellum of 20-day-old rat fetuses. So, use of antioxidant compounds can protect cellular membranes against these injuries (Onderoglu *et al.,* 1999). The comparison between non-diabetic control, diabetic control, and treated with ginseng groups in this study revealed the positive effect of ginseng extract in prevention of incidence of diabetes effects on the cerebrum and the cerebellum of rat fetuses born to mothers with diabetes, which can be attributed to

antioxidant properties of the extract. The results of this study showed that there is an increase in the number of nervous cells as well as in thickness of nervous layers in the treated group with ginseng extract compared with diabetic control group, indicating the positive effect of ginseng extract on cerebral and cerebellar tissue changes. Studies have mentioned the numerous anti-diabetic effects of ginseng plant (Lee and Yun, 2011; Hong *et al.,* 2013; Sawriss, 2011). This plant, like other medicinal herbs, has fewer side effects than chemical medications and has anti-diabetic activity and blood sugar lowering effect (Chong and Oberholzer, 1988). As mentioned earlier, one of the factors of cerebral and cerebellar anomaly generation in fetuses born to mothers with diabetes is increased fatal blood sugar levels. So, it is likely that ginseng reduces this anomaly by reducing the blood sugar.

The most important active ingredients of this plant are ginsenosides (saponins) which have triterpene structure and the pharmacological activities of the ginseng plant is attributed to these compounds (Cheng *et al.,* 2006). It has also stated that ginseng plant is considered as an adaptogen (Helms, 2004; Kitts and Hu, 2000). Adaptogenis a herbal product with antioxidant properties, which increases the body's resistance to stressors (e.g. diabetes) (Chang *et al.,* 2003). Antioxidant and anti-inflammatory activities are the other properties of the plant (Bastianetto *et al.,* 2000; Shin *et al.,* 2000). Studies have indicated that ginseng extract has positive influence on the central nervous system (Benishin *et al.,* 1991; Saito *et al.,* 1977). The results of the current research showed that ginseng extract probably due to the presence of active ingredients within itself has anti-diabetic and also anti-oxidant properties and thereby reduces the oxidative stress in the cerebrum and the cerebellum of rat fetuses born to mothers with diabetes.

Conclusion

Based on the above it can be stated that hyperglycemia occurs in fetus due to maternal diabetes, which has harmful effects on the cerebrum and the cerebellum, so that it reduces the number of cells and thickness of gray matter in 20-day-old rat fetuses. So, diabetes has non-compensatory complications and causes damage to the fetal nervous system and ginseng extract with anti-oxidant effect and reduction of blood sugar in mothers with diabetes may prevent the impact of diabetes on this system. Therefore, use of ginseng extract can considerably help to improve cerebral and cerebellar development of 20-day-old rat fetuses born to mothers with diabetes and its use is recommended to pregnant women with diabetes.

REFERENCES

Aberg A, Westbom L and Kallen B (2002). Congenital malformation among infants whose mothers had gestational diabetes or pre-existing diabetes. *Early Human Development* **61** 85-95**.**

Almeida HG, Campos JJ, Kfouri C, Tanita MT, Dias AE and Souza MM (2002). Profile of patients with diabetes type 1: insulinotherapy and self-monitoring. *Revista Da Associacao Medica Brasileira* **48**(2) 151-5.

Arafa RM (2013). Influence of ginseng, curcumin and their combination on rats suffering from diabetes and acute liver diseases. *World Applied Science Journal* **26**(10) 1391-1399.

Bastianetto S, Zheng WH and Quirion R (2000). The Ginkgo biloba extract (EGb 761) protects and rescues hippocampal cells against nitric oxide-induced toxicity: involvement of its flavonoid constituents and protein kinase C. *Journal of Neurochemistry* **74**(6) 2268- 77.

Bayreuther C, Hieronimus S, Ferrari P, Thomas P and Lebrun C (2008). Auto-immune cerebellar ataxia with anti-GAD antibodies accompanied by de novo late-onset type 1 diabetes mellitus. *Diabetes & Metabolism* **34**(4) 386-8.

Benishin CG, Lee R, Wang LC and Liu HJ (1991). Effects of ginsenoside Rb1 on central cholinergic metabolism. *Pharmacology* **42**(4) 223-9.

Chang YS, Seo EK, Gyllenhaal C and Block KI (2003). Panax ginseng: a role in cancer therapy? *Integrative Cancer Therapies* **2**(1) 13-33.

Cheng LQ, Kim MK, Lee JW, Lee YJ and Yang DC (2006). Conversion of major ginsenoside Rb1 to ginsenoside F2 by Caulobacterleidyia. *Biotechnology Letters* **28** 1121-1127.

Chong SKF and Oberholzer VG (1988). Ginseng- is there a use in clinical medicine? *Postgraduate Medical Journal* **64** 841-6.

Diveband K, Kolyli G and Saidinik F (2010). The impact of aqueous extract of walnut leaves on serum glucose and lipids of serum in diabetic rats. *Scientific Journal of Birjand Medical Sciences University* **17**(1) 11-18.

Fahimeh A (1999). Investigation on therapeutic effects of Cuminumodorumsalisb on experimental diabetes in male rats. *Abstracts of 14th Congress of Physiology and Pharmacology of Iran* 347.

Gabbe SG, Gregory RP, Power ML, Williams SB and Schulkin J (2004). Management of diabetes mellitus by obstetrician-gynecologists. *Obstetrics & Gynecology* **103**(6) 1229-34.

Helms S (2004). Cancer prevention and therapeutics: Panax ginseng. *Alternative Medicine Review* **9**(3) 259-74.

Hong BN, Ji MG and Kang TH (2013). The efficacy of red Ginseng in type 1 and type 2 diabetes in animals. *Evidence – Based Complementary and Alternative Medicine* **2013** 593181 7.

Hoveydaa N, Shieldb JPH and Garrettc C (1999). Neonatal diabetes mellitus and cerebellar hypoplasia/agenesis: report of a new recessive syndrome. *Journal of Medical Genetics* **36** 700-4.

Isah AB, Ibrahim YKE, Abdulrahman EM and Ibrahim MA (2007). The hypoglycaemic activity of the aqueous extract of *Stachytarphetaangustifolia* (Verbanaceae) in normoglycaemic and alloxan induced diabetic rats. *Pakistan Journal of Biological Science* **10**(1) 137-141.

Iwasaki H, Sato R, Shichiri M and Hirata Y (2001). A patient with type 1 diabetes mellitus and cerebellar ataxia associated with high titer of circulating anti-glutamic acid decarboxylase antibodies. *Endocrine Journal* **48**(2) 261-8.

Jafari M and Khaksar Z (2012). The influence of Aloevera extact on testicular tissue of rat fetus borntomothers with diabetes. *Scientific Journal of Yasouj Medical Sciences University* **17**(2) 149-155.

Khaksar Z, Jelodar GH and Hematian H (2010). Effect of maternal diabetes on cerebellum histomorphometry in neonatal rats. *Journal of Shaheed Sadoughi University of Medical Sciences* **18**(1) 56-63.

Kitts D and Hu C (2000). Efficacy and safety of ginseng. *Public Health Nutrition* **3**(4A) 473-85.

Lee MR and Yun BS (2011). Comparative study of Korean white, red and black Ginseng extract on cholinestrase inhibitory activity and cholinergic function. *Journal of Ginseng Research* **35**(4) 421-428.

Li WL, Zheng HC, Bukuru J and De Kimpe N (2004). Natural medicines used in traditional Chinese medical system for therapy of diabetic mellitus. *Journal of Ethnopharmacology* **92** 1-21.

Lucas MJ (2001). Diabetes complicating pregnancy. *Obstetrics & Gynecology Clinics of North America* **28** 513-36**.**

Moore T (2004). Diabetes in pregnancy. In: Creasy RK, Resnik R, Iams JD (editors). *Maternal-Fetal Medicine: Principles and Practice*, 5th edition, (USA, Philadelphia: Saunders) 1023-61.

Musen G, Lyoo IK and Sparks CR (2006). Effects of Type 1 diabetes on gray matter density as measured by voxel-based morphometry. *Diabetes* **1**(55) 326-33.

Nakamura U, Iwase M, Uchizono Y, Sonoki K, Sasaki N, Imoto H, Goto D and Iida M (2006). Rapid intracellular acidification and cell death by H2O2 and alloxan in pancreatic ß cells. *Free Radical Biology & Medicine* **40** 2047-2055.

Nikbakht M and Ghaytasi I (2006). Hypoglycemic effect of alcoholic-aqueousextract of colocynth in diabetic and neuroglysemic male rats induced by Streptozotocin. *Scientific Journal of Armaghan-e Danesh* **42** 63-71.

Northam EA, Rankins D and Lin A (2009). Central nervous system functions in youth with type 1 diabetes 12 years after disease onset. *Diabetes Care* **32**(3) 445-50.

Onderoglu S, Sozer S, Mine Erbil K, Ortac R and Lermioglu F (1999). The evolution of long-term effects of cinnamon bark and olive leaf on toxicity induced by streptozotocin administration to rats. *Journal of Pharmacy and Pharmacology* **51** 1305- 12.

Pampfer S, Vanderheyden I, McCraken JE, Vesala J and DeHertogh R (1997). Increased cell death in rat blastocysts exposed to maternal diabetes in utero and to high glucose or tumor necrosis factor alpha in vitro. *Development* **124** 4827-35.

Rafati AR, Hashemi SS and Kouhi Hosseinabadi A (2013). Evaluation of the effects of cinnamon extract on cerebellarhistomorphometric changes of rat fetus born to diabetic mothers. *Scientific Journal of Armaghan-e Danesh* **18**(6) 463-474.

Raya AO, Alfky NA and Elgazar AF (2013). Anti-obesity and anti diabetic Activities of red ginseng plant extract in obese diabetic male rats. *Global Journal of Pharmacology* **7**(4) 390-397.

Rice Ewans CA and Eurdon RM (1994). *Free Radical Damage and it's Control*, (Elsevier Amsterdam, Netherland) **113** 46-9.

Roghani M, Vaez Mahdavi M, Khalili Najaf Abadi M , Miri SR, Ansari F, Yadegari S *et al.*, (1999). The Analgesic effect of aqueous extract of fenugreek leaves in male rats with diabetes mellitus induced by Streptozotocin using Formalin test during both acute and chronic phases. *Abstracts of 14th Congress of Physiology and Pharmacology of Iran* 342.

Saito H, Tsuchiya M, Naka S and Takagi K (1977). Effects of Panax Ginseng root on conditioned avoidance response in rats. *Japanese Journal of Pharmacology* **27**(4) 509- 16.

Sawriss FAR (2011). Effect of Ginseng extract supplementation on renal function in Diabetic Rats. *Journal of Agricultural Science* **3**(2) 17- 23.

Shin HR, Kim JY, Yun TK, Morgan G and Vainio H (2000). The cancer-preventive potential of Panax ginseng: a review of human and experimental evidence. *Cancer Causes and Control* **11**(6) 565-76.

Shishtar E and Jovanovski E (2014). Effect of Korean White Ginseng on vascular and glycemic health. *Clinical Nutrition Research* **3** 89-97.

Singh BS, Westfall TC and Devascar SU (1997). Maternal diabetes-induced hyperglycemia and acute intracerebralhyperinsulinism suppress fetal brain neuropeptide Y concentrations. *Endocrinology* **138**(3) 963-9.

Tehranipour M and Khakzad MR (2008). Effect of maternal diabetes on hippocampus neuronal density in neonatal rats. *Journal of Biological Sciences* **8**(6) 1027-32.

Wyngaarden JB and Smite LH (1982). *Cecil Textbook of Medicine*, 16th edition, (W.B. Saunders Co: Philadelphia, USA) 1053-71**.**