Effect of Streptozotocin on Plasma Insulin Levels of Rats and Mice: A Meta-analysis Study

Burcu Koksal*

Inonu University, Department of Physiology, Inonu University, Faculty of Medicine, Malatya 44280, Turkey

Abstract

BACKGROUND: In the studies focusing on diabetic organisms, Streptozotocine (STZ) is a frequently used agent to induce diabetes in rats and mice. However the current studies do not represent practical importance of their statistical findings. For showing practical importance of the differences in plasma insulin levels of diabetic rats and mice induced by STZ, there should be a statistical synthesis regarding statistical findings of the studies.

AIM: The purpose of this study is to make a meta-analysis of the studies on the effect of STZ on plasma insulin levels in diabetic rats and mice.

MATERIALS AND METHODS: In this study, 39 effect sizes (37 studies) about levels of plasma insulin were analyzed by calculating individual effect sizes (d) and mean effect size.

RESULTS: The effect sizes were between -13.7 and +65.3 and the mean effect size value (+9.33) represented a large effect indicating that STZ was an effective agent to significantly decrease plasma insulin levels of diabetic rats and mice.

CONCLUSION: It can be said that the differences in plasma insulin levels between STZ-applied and no application groups has a practical importance in making animal model of diabetes.

Introduction

Nowadays, diabetes is frequently seen in society. Its prevalence is about 382 million people around the world [1]. Diabetes is characterized by insufficient secretion rate of insulin or lack of insulin activity [2, 3]. Diabetes is associated with different health problems including cardiovascular diseases, neuropathy, retinopathy, ulcers and amputations [4, 5]. Treatment of diabetes is a complex issue but some animal models were developed to understand the management as diabetes is a chronic condition [6, 7]. Over 30 years, alloxan, streptozotocin (STZ, 2-deoxy-2-(3-(methyl-3-nitrosoureido))-D-glucopyranose), high-fat diet-fed and nicotinamide are used for establishing experimental diabetes models of animal [8].

Streptozotocin is still commonly used agent to induce diabetes in rats and mice [9-12]. STZ is produced by Streptomyces sarchomogenes and STZ causes to abnormal B-cell functions by impairing glucose oxidation and decreasing insulin biosynthesis and secretion [13, 14]. Szkudelski stated that STZ dose range is larger than alloxan and other agents and only one dose is enough to induce diabetes [15]. Decrease in plasma insulin levels in animal models after STZ application is used as a sign for inducement of diabetes [16-18]. In spite of reporting significant differences in plasma insulin levels after STZ application, majority of the studies using STZ do not report practical importance or effect sizes of the differences. But there is a need to show practical importance for future decisions on dose and time of STZ application.

Based on this idea, the purpose of this study is to make a meta-analysis of the studies on the effect of STZ on plasma insulin levels in diabetic organisms.
Materials and Methods

In this study, meta-analysis approach was used to evaluate practical importance of the differences regarding plasma insulin levels of STZ-induced diabetic rats and mice. Meta-analysis is different from a review including summarizing existent literature, since meta-analysis involves statistically synthesizing results of different studies [19, 20]. For meta-analysis in this study, Cohen’s d effect size values were calculated for 37 studies and mean effect size value was found for deciding about average effect size value as an indicator of mean practical importance of the differences in plasma insulin levels induced by STZ.

Table 1: Descriptions of the publications in this study

| Publication Date | Name of Journal or Institution | Subject | STZ Amount in Application | Time between STZ Application and Plasma Insulin Measurement |
|------------------|--------------------------------|---------|---------------------------|-----------------------------------------------------|
| 2005             | Biochemical and Biophysical Research Communications | Rats | 65 mg/kg | 9 days |
| 2005             | Pharmacological Research Journal of Ethnopharmacology | Rats | 50 mg/kg | 4 weeks |
| 2005             | Journal of Biochemistry and Molecular Biology | Rats | 50 mg/kg | 6 weeks |
| 2006             | Clinical and Experimental Pharmacology and Physiology | Rats | 55 mg/kg | 21 days |
| 2006             | Journal of Health Sciences Molecular Cellular Biochemistry | Rats | 100 mg/kg | 45 days |
| 2006             | Basic & Clinical Pharmacology & Toxicology | Rats | 50 mg/kg | 45 days |
| 2006             | Pharmacology and Physiology | Rats | 55 mg/kg | 30 days |
| 2006             | Diabetes | Mice | 90-100 mg/kg | 3 weeks |
| 2006             | Physiotherapy Research International Journal of Biological Macromolecules | Rats | 50 mg/kg | 30 days |
| 2007             | Epidemiology Research Experimental Diabetes Research | Rats | 45 mg/kg | 8 weeks |
| 2008             | BMC Molecular Biology | Rats | 65 mg/kg | 15 days |
| 2009             | Atherosclerosis | Rats | 60 mg/kg | 1 week |
| 2009             | Clinical and Experimental Ophthalmology | Rats | 60 mg/kg | 1 week |
| 2010             | Phytomedicine | Rats | 60 mg/kg | 6 weeks |
| 2010             | Pharmacosgygy Res. Archives of Medical Research | Rats | 55 mg/kg | 15 days |
| 2010             | Chemicals and Biological Interactions | Rats | 60 mg/kg | 32 weeks |
| 2011             | Endocrinology | Rats | 50 mg/kg | 7 days |
| 2012             | The Journal of Pharmacology and Experimental Therapeutics | Rats | 65 mg/kg | 5 days |
| 2012             | West Virginia University, School of Medicine | Mice | 50 mg/kg | 8 weeks |
| 2012             | Turkish Journal of Medical Sciences | Rats | 45 mg/kg | 3 days |
| 2013             | BMC Complementary and Alternative Medicine | Rats | 55 mg/kg | 60 days |
| 2013             | Diabetology & Metabolic Syndrome | Rats | 50 mg/kg | 1 week |
| 2014             | BMC Pharmacological and Toxicology | Rats | 50 mg/kg | 72 hours |
| 2014             | Acta Histochemica European Journal of Pharmacology | Rats | 40 mg/kg | 2 weeks |
| 2014             | Phytomedicine | Rats | 40 mg/kg | 2 weeks |
| 2014             | Pain Medicine | Rats | 30 mg/kg | 2 weeks |
| 2014             | Pan Medicine | Rats | 40 mg/kg | 2 weeks |
| 2014             | Food and Chemical Toxicology | Rats | 40 mg/kg | 28 days |
| 2015             | International Journal of Experimental Pathology | Rats | 45 mg/kg | 24 hours |
| 2015             | Pharmacosgygy Research | Rats | 90 mg/kg | 10 weeks |
| 2015             | Nutrition | Rats | 35 mg/kg | 72 hours |
| 2015             | Renal Failure | Rats | 60 mg/kg | 5 weeks |

Selection of the Publications

In selection process of the publications PubMed, Google Scholar, Proquest and National Theses Database System were searched by using key words “Plasma insulin levels, STZ, Rats”. The time restriction for the publications was 2005-2015. In National Theses Database System no thesis was found about the keywords it might be related to system error while Proquest search showed 89 theses. However, one thesis was found appropriate. When Pubmed was searched 526 results were found. As the highest publication number, Google scholar search results gave 3960 publications.

After adding the publications to the pool, checking abstracts and content of the publications were conducted. Eventually it was determined that 37 studies reported change in plasma insulin levels of diabetic organisms and they reported 39 differences for effect size calculations across different doses of STZ. Descriptive knowledge about the publications is represented in Table 1. The titles of them can be seen in appendix (Table 3).

Calculation of Effect Sizes and Analysis

In this study plasma insulin levels measured in control and STZ groups were considered for calculating effect size values. The effect size of differences regarding plasma insulin levels were accepted as an indicator of practical importance of the differences, therefore one Cohen d formula was used to calculate effect sizes [21, 22].

\[ d = \frac{M_1 - M_2}{\sqrt{\sigma_1^2 + \sigma_2^2 / 2}} \]

After individual effect sizes per difference in each publication were calculated, mean effect size value was obtained by adding all effect sizes and dividing total effect size score into number of individual effect sizes. Hence just only one value regarding effect of STZ on plasma insulin levels was gathered.

Results

Results of the study showed that only 4 of the all individual effect sizes indicated negative values while the rest of effect sizes (n=35) was positive. Moreover one small and 38 large effect sizes were seen in the calculations. Descriptive values regarding Plasma Insulin Levels in control and STZ-induced diabetes groups, Unit of Plasma Insulin Levels and Individual Effect Sizes were shown in Table 2.

As seen in the Table 2, the individual effect sizes were between -13.7 to +65.3. The mean effect size value was found as +9.33.
The results of this study made it clearer that STZ-application is an effective way of decreasing significantly plasma insulin levels of rats and mice.

Mean effect size value calculated from the publications showed that practical importance of STZ-induced decrease in plasma insulin levels had a large effect. In other words effect size value of +9.33 refers to a large effect size [23]. Therefore the mean value of the STZ applied group is over 90 percentile of the no treatment group or control group.

The results of the study are in line with the findings of the current research studies using STZ for inducing diabetes in rats and mice [9, 10]. Sai Varsha, Thiagarajan, Manikandan and Dhanasekaran applied STZ (35mg/kg) to Male albino Wistar rats, the authors observed plasma insulin decrease in rats after 72 hours [24].

The findings of this study contribute to our understandings about practical importance of differences in plasma insulin levels induced by STZ. When looked at the number of the publications in this study, it can be seen that decisions are based on differences in the publications over 35. Hence the findings of this study make our inferences about plasma insulin level differences induced by STZ more valid rather than relying on only one study’s finding. At the same time findings of the study has a potential for informing researchers about dose and duration of STZ application to change plasma insulin levels of diabetic rats and mice. As another implication of this study, the publications analyzed in this study show characteristics of current practice about using STZ, therefore the effect sizes reported in this study also inform practice using STZ in diabetes studies.

In spite of strong sides of this study, it can be suggested that number of the publications using STZ might be increased in future studies to improving quality of inferences and to make the analysis more comprehensive. At the same time, other publications involving reports and unpublished documents should also be investigated for determining effect sizes regarding the differences about plasma insulin levels induced by STZ. Finally future studies might look at the studies published before 2005.

### Table 2: Descriptive Values regarding Plasma Insulin Levels, Unit of Plasma Insulin Levels and Individual Effect Sizes of the Differences in the Publications

| Publication Date | Name of Journal or Institution | Plasma Insulin Level | Plasma Insulin Level in STZ- induced Diabetic Group | Unit of Plasma Insulin Level | Effect Size |
|------------------|--------------------------------|----------------------|-----------------------------------------------------|-----------------------------|------------|
| 2005             | Biochemical and Biophysical Research Communications Pharmacological Research | 3.11 ± 0.07 | 0.34 ± 0.11 | ng/ml | 5.8 |
| 2005             | Journal of Pharmacology | 57 ± 4 | 58 ± 4 | μU/mL | 0.2 |
| 2005             | Journal of Ethnopharmacology | 35.40 ± 2.17 | 67.5 ± 0.15 | μg/ml | 18.7 |
| 2005             | Journal of Biochemistry and Molecular Biology | 3.2 ± 0.4 | 0.32 ± 0.1 | ng/ml | 10.2 |
| 2006             | Clinical and Experimental Pharmacology and Physiology | 15.86 ± 1.38 | 5.12 ± 0.68 | μU/mL | 9.9 |
| 2006             | Journal of Health Sciences | 16.54 ± 1.07 | 5.27 ± 0.76 | μU/mL | 12.2 |
| 2006             | Molecular and Cellular Biochemistry | 13.67 ± 1.04 | 6.99 ± 0.22 | μU/mL | 9.1 |
| 2006             | Basic & Clinical Pharmacology & Toxicology | 13.67 ± 1.04 | 6.99 ± 0.22 | μU/mL | 9.1 |
| 2006             | Clinical and Experimental Pharmacology and Physiology | 16.6 ± 2.1 | 4.3 ± 1.3 | μU/mL | 7.1 |
| 2006             | Diabetes | 0.90 ± 0.09 | 0.58 ± 0.09 | ng/ml | 3.5 |
| 2006             | Phytotherapy Research | 2.49 ± 0.26 | 0.44 ± 0.0 | ng/ml | 14.6 |
| 2006             | International Journal of Biological Macromolecules | 13.88 ± 14.52 | 4.87 ± 0.53 | μU/mL | 0.8 |
| 2007             | Journal of Ethnopharmacology | 296.21 ± 50.40 | 68.89 ± 10.12 | μg/L | 6.2 |
| 2008             | Experimental Diabetes Research | 11.8 ± 2.93 | 3.97 ± 0.86 | μg/L | 3.64 |
| 2008             | BMC Molecular Biology | 1.6 ± 0.3 | 0.7 ± 0.3 | ng/ml | 3 |
| 2008             | Atherosclerosis | 1.82 ± 0.36 | 0.05 ± 0.03 | μg/L | 7.3 |
| 2009             | Clinical and Experimental Ophthalmology | 2.23±0.18 | 0.90±0.31 | ng/ml | 4.96 |
| 2010             | Phytomedicines | 38.63±8 | 8.21±4 | μU/mL | 10.6 |
| 2010             | Pharmacognosy Res. | 390.87 ± 1.18 | 420.25 ± 2.8 | mg/dl | 13.7 |
| 2010             | Archives of Medical Research | 0.67±0.10 | 0.18±0.01 | ng/ml | 7 |
| 2011             | Chemico-Biological Interactions | 16.55 ± 1.17 | 6.07 ± 0.99 | μU/mL | 9.7 |
| 2012             | International Journal of Endocrinology | 38 ± 6 | 16 ± 2 | μU/mL | 4.9 |
| 2012             | The Journal of Pharmacology And Experimental Therapeutics | 1.69 ± 0.09 | 0.29 ± 0.03 | ng/dl | 23 |
| 2012             | West Virginia University, School of Medicine | 1.92±0.17 | 0.47±0.06 | ng/ml | 6.1 |
| 2012             | Turkish Journal of Medical Sciences | 4.28±0.83 | 0.12±0.02 | ng/ml | 7.1 |
| 2013             | BMC Complementary and Alternative Medicine | 14.2 ± 0.583 | 3.6 ± 0.509 | μU/mL | 19.6 |
| 2013             | Diabetology & Metabolic Syndrome | 4.68±0.84 | 0.65±0.14 | μU/mL | 6.7 |
| 2014             | BMC Pharmacology and Toxicology | 0.31±0.05 | 0.17±0.04 | ng/ml | 2.8 |
| 2014             | Acta Histochem | 15.41±1.21 | 8.37±1.01 | μU/mL | 6.3 |
| 2014             | European Journal of Pharamacology | 16.25±1.85 | 5.02±0.43 | μU/mL | 8.3 |
| 2014             | Phytomedicines | 15.6 ± 0.5 | 6.3 ± 0.26 | μU/mL | 23.8 |
| 2014             | Pain Medicine | 4.26 ± 0.59 | 2.28 ± 0.32 | μU/mL | 4.3 |
| 2014             | Pain Medicine | 4.26 ± 0.59 | 2.20 ± 0.30 | μU/mL | 4.5 |
| 2014             | Pain Medicine | 4.26 ± 0.59 | 2.04 ± 0.42 | μU/mL | 4.4 |
| 2014             | Food and Chemical Toxicology | 15.9 ± 1.3 | 26.1 ± 1.4 | μU/mL | 7.5 |
| 2015             | International Journal of Experimental Pathology | 6.18±0.01 | 0.95±0.12 | ng/ml | 65.3 |
| 2015             | Pharmacognosy Research | 17.66±2.91 | 83.33±6.33 | μU/mL | 13.3 |
| 2015             | Nutrition | 53.42±3.73 | 41.64±2.91 | μU/mL | 3.5 |
| 2015             | Renal Failure | 8.40±0.34 | 2.50±0.38 | ng/ml | 16.8 |

### Discussion

The results of this study made it clearer that STZ-application is an effective way of decreasing significantly plasma insulin levels of rats and mice.
the diabetic brain: Contributors to diabetes-induced brain aging. Biochimica et Biophysica Acta. 2009; 1792: 444–453.

6. Lenzen S. The mechanisms of alooaxan- and streptozotocin-induced diabetes. Diabetologia. 2008; 51: 216–226.

7. King AJF. The use of animal models in diabetes research, British Journal of Pharmacology, 2012; 166(3): 877–894.

8. Islam MS, Loots du T. Experimental rodent models of type 2 diabetes: a review. Methods and Findings in Experimental and Clinical Pharmacology. 2009; 31(4): 249-261.

9. Ibrahim DS. Abd-El-Maksoud MA. Effect of strawberry (Fragaria × ananassa) leaves extract on diabetic nephropathy in rats. International Journal of Experimental Pathology. 2015; 96(2):87–93.

10. Ngubane PS, Hadebe SI, Serumula MR, Musabayane CT. The effects of transdermal insulin treatment of streptozotocin-induced diabetic rats on kidney function and renal expression of glucose transporters. Renal Failure. 2015; 37(1): 151-159.

11. Willecke F. et al. Lipolysis, and not hepatic lipogenesis, is the primary modulator of triglyceride levels in streptozotocin-induced diabetic mice. Arteriosclerosis, Thrombosis, and Vascular Biology. 2015; 35: 102–110.

12. Dominguez JM, Yorek MA, Grant MB. Combination therapies prevent the neuropathic, proinflammatory characteristics of bone marrow in streptozotocin-induced diabetic rats. Diabetes. 2015; 64 (2): 643-653.

13. Nukatsuka M, Yoshimura Y, Nishim AD, Kawada J. Importance of the concentration of ATP in rat pancreatic beta cells in the mechanism of streptozotocin-induced cytotoxicity. Journal of Endocrinology. 1990; 127: 161-165.

14. Bedoya FJ, Solano F, Lucas M. N-monomethyl-arginine and nicotinamide prevent streptozotocin-induced double strand DNA break formation in pancreatic rat islets. Experientia. 1996; 52: 344-347.

15. Szkudelski T. The mechanism of alloxan and streptozotocin action in b cells of the rat pancreas, Physiological Research. 2001; 50: 536-546.

16. Daisy P, Balasubramanian K, Rajalakshmi M, Eliza J, Selvaraj J. Insulin mimetic impact of Catechin isolated from Cassia fistula on the glucose oxidation and molecular mechanisms of glucose uptake on Streptozotocin-induced diabetic Wistar rats. Phytomedecine. 2010; 17(1): 28-36.

17. Dang JK, Wu Y, Cao H, Meng B, Huang CC, Chen G, Li J, Song XJ, Lian QQ. Establishment of a rat model of type II diabetic neuropathic pain. Pain Medicine. 2014; 15(4): 637-646.

18. Patel SB, Santati D, Patel V, Shah M. Anti-diabetic effects of ethanol extract of Blyonia laciniosa seeds and its saponins rich fraction in neonatal streptozotocin-induced diabetic rats. Pharmacognosy Research. 2015; 7(1): 92-99.

19. Fleis JL. The statistical basis of meta-analysis. Statistical Methods in Medical Research. 1993; 2: 121–145.

20. Maksimovic J. The application of meta-analysis in educational research. Facta Universitatis. 2011; 10 (1): 45-55.

21. Rosnow RL, Rosenthal R Computing contrasts, effect sizes, and counternulls on other people’s published data: General procedures for research consumers. Psycological Methods. 1996; 1: 331-340.

22. Cumming, G. Understanding the new statistics: Effect sizes, confidence intervals, and meta-analysis. New York, NY: Routledge, 2012.

23. Cohen, J. Statistical power analysis for the behavioral sciences (2nd ed.). Hillsdale, NJ: Lawrence Erlbaum Associates,1988.

24. Sai Varsha MKN, Thiagarajan R, Manikandran R, Dhanasekaran G. Vitamin K1 alleviates streptozotocin-induced type 1 diabetes by mitigating free radical stress, as well as inhibiting NF-κB activation and iNOS expression in rat pancreas. Nutrition. 2015; 31: 214–222.

**Appendix**

**Table 3: Titles of the publications**

| Publication Date | Titles of the publications |
|------------------|---------------------------|
| 2005             | Streptozotocin-induced diabetes in the rat is associated with enhanced tissue hydrogen sulfide biosynthesis |
| 2005             | Glucocortic, a flavonoid antioxidant, prevents and protects streptozotocin-induced oxidative stress and cell damage in rat pancreas |
| 2005             | Study of the hypoglycaemic activity of Lepidium sativum L. aqueous extract in normal and diabetic rats |
| 2005             | Red wine prevents brain oxidative stress and nephropathy in streptozotocin-induced diabetic rats |
| 2005             | Beneficial effects of Aloe vera leaf gel extract on lipid profile status in rats with streptozotocin diabetes |
| 2005             | Anti-diabetic activity of fruits of terminalia chebula on streptozotocin induced diabetic rats |
| 2006             | improves the antioxidant status in streptozotocin-induced diabetic rat tissues |
| 2006             | Antihyperglycemic and antioxidant effect of rutin, a polyphenolic flavonoid, in streptozotocin-induced diabetic wistar rats |
| 2006             | Biochemical evaluation of antidiabetic properties of some commonly used Indian plants on streptozotocin-induced diabetes in experimental rats |
| 2006             | Glucose inhibition of dipeptidyl peptidase-4 with a sitagliptin analog preserves pancreatic-cell mass and function in a rodent model of type 2 diabetes |
| 2006             | Effect of Japanese radish (Raphanus sativus) sprout (Kawara-daikon) on carbohydrate and lipid metabolites in normal and streptozotocin-induced diabetic rats |
| 2007             | Protective effect of Lysium barbarum polysaccharides on streptozotocin-induced oxidative stress in rats |
| 2007             | Effect of Scirpecarya birea (Anacardiacae) stem bark methanolic chloroform/methanol extract on streptozotocin-diabetic rats |
| 2008             | The Characterization of High-Fat Diet and Multiple Low-Dose Streptozotocin Induced Type 2 Diabetes Rat Model |
| 2008             | Genomic actions of 1,25-dihydroxyvitamin D3 on insulin receptor gene expression, insulin receptor number and insulin activity in the kidney, liver and adipose tissue of streptozotocin-induced diabetic rats |
| 2008             | Mechanisms underlying recouping of eNOS by HMG-CoA reductase inhibition in a rat model of streptozotocin-induced diabetes mellitus |
| 2009             | Effect of N-acetylprocollagen on the early expression of inflammatory markers in the retina and plasma of diabetic rats |
| 2009             | Insulin mimetic impact of Catechin isolated from Cassia fistula on the glucose oxidation and molecular mechanisms of glucose uptake on Streptozotocin-induced diabetic Wistar rats |
| 2009             | Anti hyperglycemic activity of Catharanthus roseus leaf powder in streptozotocin-induced diabetic rats |
| 2009             | Effect of Dipeptidyl Peptidase-IV (DPP-IV) Inhibitor (Vildagliptin) on Peripheral Nerves in Streptozotocin-induced Diabetic Rats |
| 2010             | Insulin-secretagogue, antihyperglycemic and other protective effects of gallic acid isolated from Terminalia bellirica Roxb. in streptozotocin-induced diabetic rats |
| 2010             | Intermittent Fastening Modulation of the Diabetic Syndrome in Streptozotocin-Injected Rats |
| 2010             | Dipeptidyl Peptidase IV Inhibitor Attenuates Kidney Injury in Streptozotocin-Induced Diabetic Rats |
| 2010             | Examination of novel cardiac mechanisms influencing mitochondrial proteomes during diabetes mellitus |
| 2010             | Effects of lycopen on plasma glucose, insulin levels, oxidative stress, and body weights of streptozotocin-induced diabetic rats |
| 2010             | Anti-diabetic, anti-oxidant and anti-hyperglycemic activities of Melastoma malabathricum Linn. leaves in streptozotocin-induced diabetic rats |
| 2010             | The effect of a novel curcumin derivative on pancreatic islet regeneration in experimental type-1 diabetes in rats (long term study) |
| 2010             | CNX-011-67, a novel GPR40 agonist, enhances glucose responsiveness, insulin secretion and insulin content in n-STZ rats and in islets from type 2 diabetic patients |
| 2010             | B-Caryophyllene, a natural sesquiterpene, modulates carbohydrate metabolism in streptozotocin-induced diabetic rats |
| 2010             | Fisetin improves glucose homeostasis through the inhibition of gluconeogenic enzymes in hepatic tissues of streptozotocin induced diabetic rats |
| 2010             | Efficacy of natural diacigenin on cardiovascular risk, insulin secretion, and beta cells in streptozotocin (STZ)-induced diabetic rats |
| 2010             | Establishment of a Rat Model of Type II Diabetic Neuropathic Pain |
| 2010             | Polyphenols-rich Gympsis tetragonalob (L.) Taub. bears show hypoglyeemic and β-cells protective effects in type 2 diabetic rats |
| 2010             | Effect of strawberry (Fragaria × ananassa) leaves extract on diabetic nephropathy in rats |
| 2010             | Anti-diabetic effects of ethanol extract of Blyonia laciniosa seeds and its saponins rich fraction in neonatal streptozotocin-induced diabetic rats |
| 2010             | Vitamin K1 alleviates streptozotocin-induced type 1 diabetes by mitigating free radical stress, as well as inhibiting NF-κB activation and iNOS expression in rat pancreas |
| 2010             | The effects of transdermal insulin treatment of streptozotocin-induced diabetic rats on kidney function and renal expression of glucose transporters |

OA Maked J Med Sci. 2015 Sep 15; 3(3):380-383.