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The effect of a formulation containing honey, black cumin, propolis and royal jelly on blood glucose level and pancreatic β-cells of streptozotocin-induced diabetic rats

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ABSTRACT

A formulation containing 40% of honey, 30% of black cumin, 20% of propolis and 10% of royal jelly has been available in the market for the treatment of diabetes. Although each content of the formulation is proven to possess antioxidant and antihyperglycemic activities, its combination effect has not been evaluated yet. The aim of this study was to evaluate the effect of this formulation on blood glucose level and pancreatic β-cells of streptozotocin (STZ)-induced diabetic rats. Thirty six male Wistar rats (*Rattus novergicus*) aged 11 weeks with body weight 100-150 g were used in this study. The rats were divided into 6 groups with 6 rats in each group. Group 1 was non diabetic rats that were given aquadest. Group 2 was diabetic rats that were given aquadest. Group 3 was diabetic rats that were given metformin at dose of 45 mg/kg BW. Group 4-6 were diabetic rats that were given formulation tested at dose of 3, 6 and 12 mL/kg BW, respectively. All rats were induced by intraperitoneal injection of STZ at 60 mg/kg BW and diabetic rats were then orally administered the formulation tested or metformin twice daily for 14 days. Blood glucose level was monitored on day 10 and 17 after STZ induction. Rats were sacrificed and pancreas samples were taken for histopathological examination. The results showed that the blood glucose level decreased significantly after seven days of treatment with metformin or fomulation tested and continued after 14 days of treatment. The blood glucose level of diabetic rats after 14 days of treatment returned to the normal level. The vacuolization of the pancreatic β-cells of diabetic rats treated with metformin or with formulation tested were lower than untreated diabetic rats but still higher than non diabetic rats. In conclusion, the formulation tested has antihyperglicemic and protective effect on β-cells damage in diabetic rats.

ABSTRAK

Sebuah formulasi yang mengandung 40% madu, 30% jinten hitam, 20% propolis dan 10% royal jeli telah tersedia di pasaran untuk mengobati diabetes. Meskipun masing-masing kandungan formulasinya telah dibuktikan mempunyai aktivitas antioksidan dan antihiperglikemi, tetapi efek kombinasinya belum pernah dikaji. Penelitian ini bertujuan untuk mengkaji efek pemberian fromulasi tersebut pada gula darah dan sel-β pankreas tikus diabetes yang diinduksi streptozotosin (STZ). Tiga puluh enam tikus jantan Wistar (*Rattus novergicus*) berumur 11 minggu dengan berat badan 100-150 g digunakan dalam penelitian ini. Tikus dibagi 6 kelompok dengan masing-masing kelompok 6 ekor. Kelompok 1 adalah tikus normal yang diberi akuades. Kelompok 2 adalah tikus

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diabetes yang diberi akuades. Kelompok 3 adalah tikus diabetes yang diberi metformin dosis 45 mg/kg BB. Kelompok 4-6 adalah tikus diabetes yang diberi formulasi dosis 3, 6 dan 12 mL/kg BB. Tikus diinduksi STZ intraperitonial dengan dosis 60 mg/kg BB. Tikus diabetes kemudian diberi metformsin atau formulasi uji dua kali sehari selama 14 hari. Kadar gula darah dimonitor pada hari ke 10 dan 17 setelah induksi STZ. Tikus dikorbankan dan diambil pankreasnya untuk pemeriksaan histopatologi. Hasil penelitian menunjukkan kadar gula darah menurun secara bermakna setelah tuju hari perlakuan dengan metformin atau formulasi uji. Setelah hari ke 14 perlakuan, kadar gula darah kembali dalam kondisi normal. Vakuolisasi sel-β pankreas tikus diabetes yang diberi metformin atau formulasi uji lebih rendah dari pada tikus diabetes yang tidak diobati tetapi masih lebih tinggi dari tikus normal. Dapat disimpulkan, formulasi uji mempunyai efek antihiperglikemia dan efek protektif terhadap kerusakan sel-β pankreas tikus diabetes.

Keywords: diabetic rats - honey - black cumin - propolis - royal jelly - antihyperglicemic

INTRODUCTION

The prevalence of diabetes mellitus (DM) is increasing due to population growth, aging, urbanization, and increasing prevalence of obesity and physical inactivity. World Health Organization (WHO) estimated that the prevalence of DM in the world in 2000 reached 171,228 million and it will be 366,212 million in 2030**.** In Indonesia, it was estimated that the number of people with DM in 2000 increased from 8.4 million to 21.3 million in 2030. Indonesia is the fourth country with highest number of people with DM in the world for 2000 and 2030 after India, China dan America.[1]

Diabetes mellitus is characterized with hyperglycemia that is associated with pancreatic β-cells damage occurring together with insulin resistance. Normal pancreatic â-cells can compensate for insulin resistance by increasing insulin secretion. However, insufficient compensation leads to the onset of glucose intolerance.[2] Hyperglycemia generates from reactive oxygen species (ROS) leading to the increased oxidative stress in variety of tissues including pancreas. The absence of endegenous antioxidant compensates the increase of oxidative stress causing cellular damage that is responsible for diabetes complications.[3]

Some formulations with natural products have been used traditionally to treat DM since a long time ago. One of the formulations containing 40% of honey, 30% of black cumin, 20% of propolis and 10% of royal jelly has been available in the market for the treatment of diabetes. Although each content of the formulation is proven to possess antioxidant and antihyperglycemic activities, however its combination effect has not been evaluated, yet. Honey in combination with glibenclamide and metformin has an antioxidant protective effect in pancreas of STZ-induced diabetic rats, while black cumin (*Nigella sativa*) has a protective effects on β-cells damage in STZ-induced diabetic rats.[4,5] Moreover, propolis possesses antihyperglycemic activity in STZ-induced diabetic rats[6,7] while royal jelly possesses antioxidant and antihypercholesterolemic activities.[8]

It is apparent that the different natural products would work by different mechanism in the decrease of hyperglycemic in diabetic rats. However, very few studies are conducted to evaluate a combination activity of the different natural products as antihyperglycemic in diabetic rats. This study was conducted to evaluate the effect of a formulation containing honey, black cumin, propolis and royal jelly on blood glucose level of STZ-induced diabetic rats. Its protective effect of this formulation on the pancreatic β-cells damage was also investigated.

MATERIALS AND METHODS

Animals and materials

This study was started after obtaining an approval from the the Medical and Health Research Ethics Committee, Gadjah Mada University, Yogyakarta. Thirty six male Wistar rats (*Rattus novergicus*) aged 11 weeks with body weight 100-150 g obtained from the Integrated Research and Testing Laboratory, Universitas Gadjah Mada, Yogyakarta were used in this study. The rats were housed at room temperature under 12 hour cycles of dark and light and were allowed standard food and water *ad libitum*. The rats were divided into 6 groups with 6 rats in each group. Group 1 as normal contol was non diabetic rats that were given aquadest. Group 2 as negative control was diabetic rats that were given aquadest. Group 3 as positive control was diabetic rats that were given metformin at dose of 45 mg/kg BW. Group 4-6 as treatment groups were given formulation tested at dose of 3, 6 and 12 mL/kg BW, respectively.

The formulation tested was the mixture of 40% honey, 30% black cumin, 20% propolis, and 10% royal jelly obtained from CV Cahya Sejati, Madiun. Streptozotocine was obtained from Sigma Biomedical Inc. USA, and metformin was obtained from Hexpharm Jaya, Indonesia.

Induction of hyperglycemic and formulation administration

Rats were used for the study after an acclimatization period of one week and were fasted for 18 hours before experimental sessions but allowed to have a free access to water during the experiment. Before STZ injection, blood sample was taken from orbital sinus and blood glucose level was determined by using GOD PAP method. Hyperglycemia was induced by intraperitoneal injection of STZ at 60 mg/kg BW, freshly dissolved in citrate buffer (0.01 M and pH 4.5). The day of STZ injection was designated as day 0. Development of diabetes was confirmed by measuring blood glucose level three days after STZ injection (day 3). Rats with blood glucose level higher than 200 mg/dL were considered to be diabetic[9] and selected for the experiment. The diabetic rats were then orally administered the formulation tested or metformin twice daily for 14 days. Blood glucose level was monitored on day 10 and 17 after STZ injection.

Histopathological examination of pancreatic β-cells

At the end of experiment, rats were sacrificed and a midline abdominal incision was made. Pancreases were removed from the mice and fixed in a solution of 10% buffered para-formaldehyde, dehydrated in a graded ethanol series, cleared in xylene and then embedded in paraffin wax. Approximately 5-μm sections were prepared and stained with Gomori's chrome alum stain for detection of pancreatic β-cells.[10] Olympus light microscopy was used to examine the pancreatic β-cells. Slides were photographed using Olympus digital camera. The pancreatic β-cells were counted in chome alum slides under 400 high power fields. In this study, the number of pancratic β-cells was assessed by counting the number of vacuolated cytoplasm of the blue stained cells inside one islet in the field. A minimum of 5 randomly selected fields per section from each rat were analiysed.

Statistical analysis

All results were expressed as mean ± standar deviation (SD). Blood glucose were compared by a one or two-way ANOVA. A $p<0.05$ was considered to be statistically significant.

RESULTS

Blood glucose level of non diabetic, diabetic, metformin treated diabetic, formulation treated diabetic rats groups on day 0, 3, 10 and 17 after STZ injection are shown in TABLE 1 and FIGURE 1. The blood glucose level of all groups before STZ injection (day 0) were in normal level. Three days after STZ injection (day 3), rats were diabetic as demonstrated with a blood glucose level higher than 200 mg/dL. Seven days (day 10) after treatment with metformin or formulation tested, blood glucose level was significantly reduced compared with before treatment (day 0) ($p<0.05$) and was in a normal state (<200 mg/mL). Moreover, blood glucose level of rats after treatment with metformin or formulation tested were significantly lower than blood glucose level of untreated diabetic rats ($p<0.05$). The decrease of blood glucose level of rats continued on day 17 after treatment with metformin and formulation tested, whereas the blood glucose level of untreated diabetic rats were similar on day 3, 10 and 17 after STZ injection.

TABLE 1. Blood glucose level of non diabetic, diabetic, metformin treated diabetic, formulation treated diabetic rats groups on day 0, 3, 10 and 17 after STZ injection

Groups	Blood glucose level (Mean ± SD mg/dL)			
	Day 0	Day 3	Day 10	Day 17
1. Non diabetic rats + aquadest	77.52±1.30	78.16 ±1.88	82.30±1.62	98.94±1.14
2. Diabetic rats + aquadest	89.04±5.68	236.37±9.70	228.70±20.49	216.94±18.83
3. Diabetic rats + metformin 45 mg/kg BW	91.38±6.85	238.60±9.33	111.42±3.69	104.01±1.92
4. Diabetic rats + formulation 3 mL/kg BW	77.31±4.78	232.28±11.53	193.26±15.90	155.50±22.31
5. Diabetic rats+formulation 6 mL/kg BW	83.68±2.93	231.86±12.06	154.03±11.08	131.28±14.80
6. Diabetic rats+formulation 12 mL/kg BW	94.15±3.76	236.21±13.35	125.14±18.97	115.14±16.26

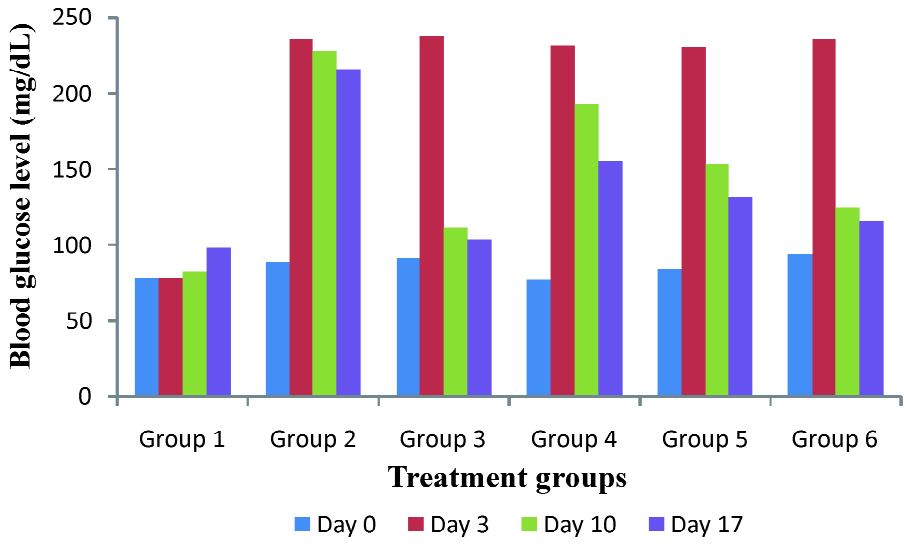

FIGURE 1. Blood glucose level of each rat group on day 0, 3, 10 and 17 after STZ injection. Group 1: non diabetic rats; Group 2: diabetic rats; Group 3: diabetic rats + metformin 45 mg/kg BW; Group 4: diabetic rats + formulation 3 mL/kg BW; Group 5: diabetic rats + formulation 6 mL/kg BW; Group 6: diabetic rats + formulation 12 mL/kg BW.

Pancreatic β-cells of a normal rat, diabetic rat and diabetic rat after treatment with metformin and formulation after Gomori's chrome alum staining are presented in FIGURE 2.

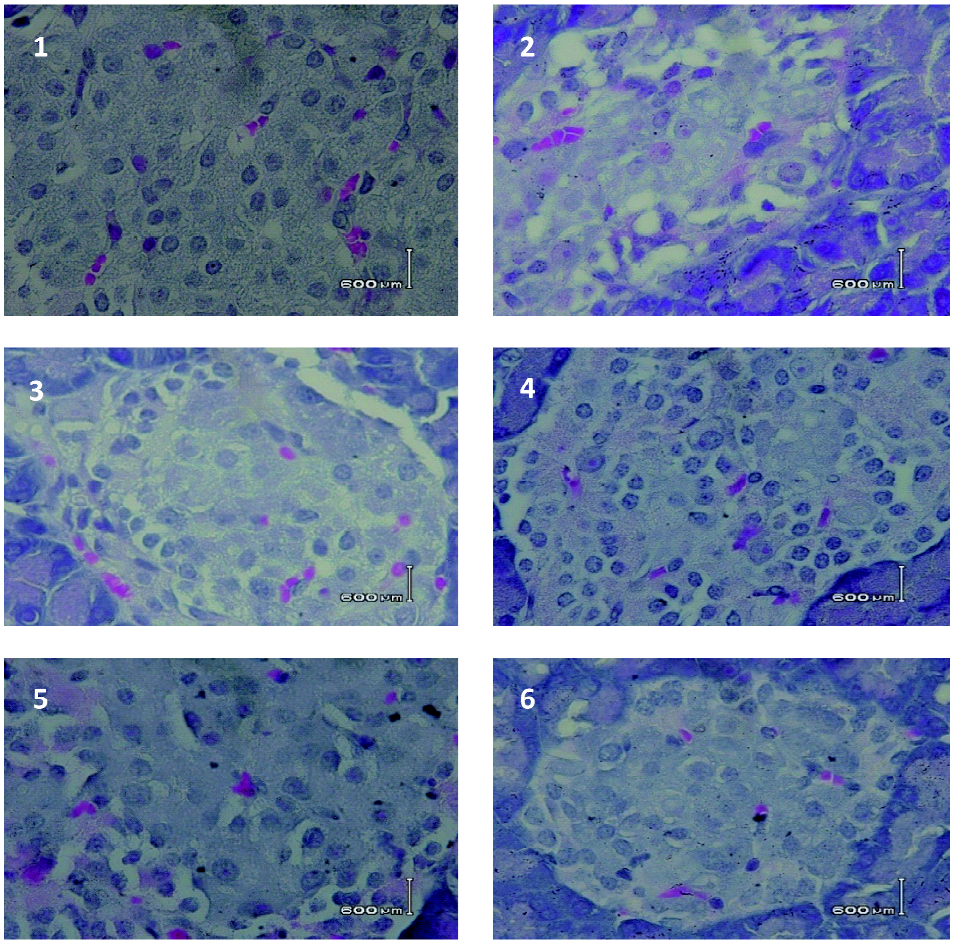

FIGURE 1. Pancreatic β-cells of 1) non diabetic rat, 2) untreatet diabetic rat, 3) metformin treated diabetic rat at 9 mg/kg BW, 4) formulation treated diabetic rat at 12 mL/kg BW, 5) formulation treated diabetic rat at 6 mL/kg BW, 6) formulation treated diabetic rat at 3 mL/kg BW

The average cytoplasmic vacuolization of the pancreatic β-cells of non diabetic rats, untreated diabetic rats and rats after 14 days administration with metformin and formulation tested are shown in TABLE 2. The biggest number of cytoplasmic vacualization of pancreatic β-cells was observed on untreated diabetic rats, while the lowest cytoplasmic vacuolization was observed on non diabetic rats ($p<0.05$). The cytoplasmic vacuolization of the pancreatic β-cells on diabetic rats treated with metformin or with formulation tested were lower than untreated diabetic rats but still higher than non diabetic rats ($p<0.05$). The lowest vacuolization of pancreatic β-cells of diabetic rats after administration of formulation tested was observed at dose 3 mL/kg BW.

TABLE 2. The cytoplasmic vacuolization of the pancreatic β-cells of non diabetic rats, untreated diabetic rats and rats after 14 days administration with metformin and formulation tested

Groups	The amount of the vacuole (mean ± SD)
Non DM rats + aquadest	15 ± 8
DM rats + aquadest	168 + 23
DM rats + metformin 45 mg/kg BW	116 ± 20
DM rats + formulation 3 mL/kg BW	65 ± 16
DM rats + formulation 6 mL/kg BW	112 ± 12
DM rats + formulation 12 mL/kg BW	97 ± 26

DISCUSSION

Before STZ induction, the blood glucose level of rats used in this study was still in a normal value range. As reported by Butler[11], the normal blood glucose level of healthy rats varies between 50 to 135 mg/dL depending on the type of food consumed and time since the last meal. Three days after STZ induction, the blood glucose level increased significantly from 231 to 238 mg/dL (TABLE 1) indicating that the rats were diabetic.[9]

Streptozotocin is an antibiotic isolated from *Streptomyces achromenes* that is commonly used to induce diabetic in experimental model animal. Streptozotocin possesses â-cell cytotoxic effect that is associated with the inhibition of free radical scavenger enzymes, thereby enhancing the production of superoxide radical. The diabetic animal caused by STZ is associated with the generation of ROS causing oxidative damage of β-cell.[12,13]

This study was conducted to evaluate effects of a formulation containing containing honey, black cumin, propolis and royal jelly on blood glucose level and pancreatic β-cells damage in STZ-induced diabetic rats. The results showed that the blood glucose level of all STZ-induced diabetic rats decreased significantly after seven days of treatment with fomulation tested (day 10) and continued decreasing after 14 days of treatment (day 17) to the normal level (<200 mg/dL). Therefore, it was indicated that the formulation has antihyperglicemine effect.

The antihyperglicemic effect of the formulation might be resulted from the combination of each effect of all the contents in the formulation. The activity of the content of the formulation as antioxidant and antihyperglicemic has been evaluated by some authors. Honey is reported to be able to significantly reduce blood glucose level in alloxan-iduced and STZ-induced diabetic rats.[4,14,15] The possible mechanism of action of honey as antihyperglycemic is reviewed by Erejuwa *et al*.[16] The potential mechanism of actions of honey may be based on its non antioxidant and antioxidant effect of constituents. Honey increases plasma fructose level that leads to increased hepatic glucose uptake by activating glucokinase. Moreover, some of minerals in honey such as chromiun are recognized for their role in the reduction of elevated blood glucose, and maintenance of normal glucose tolerance and insulin secretion from the pancreatic â-cells. A number of studies have shown that honey can scavenge free radicals, ameliorate oxidative stress in the pancreas, protect the pancreas against oxidative damage and thus enhance insulin secretion resulting in improved glycemic control.

The effect of antihyperglicemic in black cumin (*Nigella sativa*) in diabetic animal models has been reported.[5,17] The antihyperglicemic effect of *N. sativa* is mediated through activation of the AMPK pathway that increased muscle Glut4 content.[18] *Nigella sativa* also reported to be able to decrease oxidative stress, preserve the integrity and protect the damage of pancreatic β-cell that is caused by hyperglicemic in diabetic rats.[19,20] In addition, *N. sativa* is reported to inhibit intestinal glucose absorption and improves glucose tolerance in rats.[21]

The effect of propolis as antihyperglycemic in STZ-induced diabetic rats has been also reported.[6,7,22] The antihyperglycemic effect of propolis is mediated through reduction of expression of glucose-6-phosphatase through inhibition of Y279 and Y216 autophosphorylation of GSK-3α/β in HepG2 cells.[23] Propolis is also reported to possess β-cell protective effect against the toxicity of STZ in rats. The free radical scavenging effect together with IL-1β and nitric oxide (NO) synthase inhibitory effect are thought to be the main factors for the protective effect of propolis against STZ toxicity.[24]

Royal jelly has been proven to possess antioxidant and antihypercholesterolemic activities.[8] Royal jelly peptides are isolated from hydrolysates of water-soluble royal jelly proteins peptides to inhibit lipid peroxidation both *in vitro* and *in vivo*.[25] Antioxidant effect of royal jelly is used against oxidative stress of the kidney and liver injury caused by cytotoxic agents.[26,27]

In this study, most of the pancreatic â-cells of non diabetic rats were stained deep blue in the cytoplasma as previously reported by Rifaai *et al*.[28] On untreated diabetic rats, degenerative changes of the pancreatic β-cells were observed as indicated by a significant decrease in the density of bluish stained and the increase in cytoplasmic vacuolization of β-cells ($p<0.05$).[29] Treatment with metformin or formulation tested was able to significantly decrease the cytoplasmic vacuolization of β-cells ($p<0.05$) although it was still higher than on non diabetic rats. It was thought that the formulation has antihyperglicemic effect through its protective effect of β-cells damage.

CONCLUSION

In conclusion, the formulation tested containing 40% of honey, 30% of black cumin, 20% of propolis and 10% of royal jelly has antihyperglicemic effect in STZ-induced diabetic rats. Moreover, the fromulation also has a protective effect on β-cells damage in the diabetic rats. In addition, further study in order to evaluate the toxicity of the formulation should be conducted.

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REFERENCES

1. Wild S, Roglic G, Green A, Sicree R, King H. Global preevalence of diabetes: estimates for the year 2000 and projetions for 2030. Diabetes Care 2004; 27(5):1047-53.
2. Kaneto H, Kajimoto Y, Miyagawa JI, Matsuoka TA, Fujitani Y, Umayahara Y, *et al*. Beneficial effects of antioxidants in diabetes possible protection of pancreatic β-cells against glucose toxicity. Diabetes 1999; 48(12):2398-406.
3. Evans JL, Goldfine ID, Maddux BA, Grodsky GM. Oxidative stress and stress-activated signaling pathways: a unifying hypothesis of type2 diabetes. Endocr Rev 2002; 23(5):599-622.
4. Erejuwa OO, Sulaiman SA, Wahab MS, Salam SK, Salleh MS, Gurtu S. Antioxidant protective effect of glibenclamide and metformin in combination with honey in pancreas of streptozotocin-induced diabetic rats. Int J Mol Sci 2010; 11(5):2056-66.
5. Kanter M, Akpolat M, Aktas C. Protective effects of the volatile oil of *Nigella sativa* seeds on beta-cell damage in streptozotocin-induced diabetic rats: a light and electron microscopic study. J Mol Histol 2009; 40(5-6):379-85.
6. Zhu W, Chen M, Shou Q, Li Y, Hu F. Biological activities of chinese propolis and brazilian propolis on streptozotocin-induced type 1 diabetes mellitus in rats. Evid Based Complement Alternat Med 2011; 468529. Doi: 10.1093/ecam/neq025.
7. Li Y, Chen M, Xuan H, Hu F. Effects of encapsulated propolis on blood glycemic control, lipid metabolism, and insulin resistance in type 2 diabetes mellitus rats. Evid Based Complement Alternat Med 2012; 981896. doi: 10.1155/2012/981896.

8. Viuda-Martos M, Ruiz-Navajas, Fernández-López J, Pérez-Álvarez JA. Functional properties of honey, propolis, and royal jelly. J Food Sci 2008; 73(9):R117-24.
9. Prince SM, Venugopal MP. Anti-oxidant action of *Tinospora cordifolia* root extract in alloxan diabetic rats. Phytother Res 2001; 15(3): 213-8.
10. Carleton HM., Drury RAB, Wallington EA. Carlton's histological technique, 5th eds. New York: Oxford University Press, 1980: 173-174
11. Butler LK. Regulation of blood glucose levels in normal and diabetic rats. In: Goldman CA edior. Tested studies for laboratory teaching. Austin: University of Texas, 1995: 181-202.
12. Coskun O, Kanter M, Korkmaz M, Oter S. Quercetin, a flavonoid antioxidant, prevents and protects streptozotocin-induced oxidatives stress and â-cell damage in rat pancreas. Phamacol Res 2005; 51(2):117-23.
13. Szkudelski T. The mechanism of alloxan and streptozotocin action in â-cells of the rat pancreas. Physiol Res 2001; 50(6):537-46.
14. Erejuwa OO, Gurtu S, Sulaiman SA, Ab Wahab MS, Sirajudeen KN, Salleh MS. Hypoglycemic and antioxidant effects of honey supplementation in streptozotocin-induced diabetic rats. Int J Vitam Nutr Res 2010; 80(1): 74-82.
15. Erejuwa OO, Sulaiman SA, Wahab MS, Sirajudeen KN, Salleh MS, Gurtu S. Glibenclamide or metformin combined with honey improves glycemic control in streptozotocin-induced diabetic rats. Int J Biol Sci 2011; 7(2): 244-52.
16. Erejuwa OO, Sulaiman SA, Wahab MS. Honey: a novel antidiabetic agent. Int J Biol Sci 2012; 8(6):913-34.
17. Salama RH. Hypoglycemic effect of lipoic acid, carnitine and *Nigella sativa* in diabetic rat model. Int J Health Sci 2011; 5(2):126-34.
18. Benhaddou-Andaloussi A, Martineau L, Vuong T, Meddah B, Madiraju P, Settaf A, *et al.* The *in vivo* antidiabetic activity of *Nigella sativa* is mediated through activation of the AMPK pathway and increased muscle Glut4 content. Evid Based Complement Alternat Med 2011; 538671. Doi: 10.1155/2011/538671.
19. Abdelmeguid NE, Fakhoury R, Kamal SM, Al Wafai RJ. Effects of *Nigella sativa* and thymoquinone on biochemical and subcellular changes in pancreatic β-cells of streptozotocin-induced diabetic rats. J Diabetes 2010; 2(4):256-66.
20. Kanter M, Akpolat M, Aktas C. Protective effects of the volatile oil of *Nigella sativa* seeds on β-cell damage in streptozotocin-induced diabetic rats: a light and electron microscopic study. J Mol Histol 2009; 40(5-6):379-85.
21. Meddah B, Ducroc R, El Abbes Faouzi M, Eto B, Mahraoui L, Benhaddou-Andaloussi A, et al., Martineau LC, Cherrah Y, Haddad PS. *Nigella sativa* inhibits intestinal glucose absorption and improves glucose tolerance in rats. J Ethnopharmacol 2009; 121(3):419-24.
22. Al-Hariri M, Eldin TG, Abu-Hozaifa B, Elnour A. Glycemic control and anti-osteopathic effect of propolis in diabetic rats. Diabetes Metab Syndr Obes 2011; 4:377-84.
23. Kang LJ, Lee HB, Bae HJ, Lee SG. Antidiabetic effect of propolis: reduction of expression of glucose-6-phosphatase through inhibition of Y279 and Y216 autophosphorylation of GSK-3α/β in HepG2 cells. Phyrother Res 2010; 24(10):1554-61.
24. Matsushige K, Basnet P, Hase K, Kadota S, Tanaka K, Namba T. Propolis protects pancreatic β-cells against the toxicity of streptozotocin (STZ). Phytomedicine 1996; 3(2):203-9.
25. Guo H, Ekusa A, Iwai K, Yonekura M, Takahata Y, Morimatsu F. Royal jelly peptides inhibit lipid peroxidation *in vitro* and *in vivo*. J Nutr Sci Vitaminol 2008; 54(3):191-5.
26. Karadeniz A, Simsek N, Karakus E, Yildirim S, Kara A, Can I, *et al.* Royal jelly modulates oxidative stress and apoptosis in liver and kidneys of rats treated with cisplatin. Oxid Med Cell Longev 2011; 981793. Doi: 10.1155/2011/981793.
27. Cemek M, Yýlmaz F, Büyükokuroðlu ME, Büyükben A, Aymelek F, Ayaz A. Serum and liver tissue bio-element levels, and antioxidant enzyme activities in carbon tetrachloride-induced hepatotoxicity: protective effects of royal jelly. J Med Food 2012; 15(8):747-52.
28. Rifaai RA, El-Tahawy NF, Saber EA, Ahmed R. Effect of quercetin on the endocrine pancreas of the experimentally induced diabetes in male albino rats. J Diabetes Metab 2012; 3:182. Doi:10.4172/2155-6156.1000182
29. O'Brien TD, Butler PC, Westernak P. Islet amyloid polypeptide; a review of its biology and potential roles in the pathogenesis of diabetes mellitus. Vet Pathol 1993; 30:317-32.