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**Effect of Propolis on Blood Glycemic Control and Lipid
Metabolism in Diabetic Rabbits**

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Abstract

Propolis is a honeybee product that has gained popularity in alternative medicine, due to its biological properties and it has been intensively used in health foods. This study was carried out to investigate the effect of propolis on some biochemical parameters in alloxan-induced diabetic rabbits. Diabetes was induced in all rabbits, except normal control, by a single dose of Alloxan (150 mg/kg, I.V.). Rabbits with glycaemia were treated with alcoholic extract of propolis for 23 days. The marked significant differences ($p < 0.05$) in weights of body, liver and the biochemical values which included glucose, total protein, triglycerides and total cholesterol are recorded in comparison with control group. The results indicate a significant decrease ($P < 0.05$) in the body weight of alloxan-induced diabetic rabbits in comparison with control group, while there were significant increases in the weights of liver. Also, biochemical changes showed significant increases ($P < 0.05$) in glucose, total protein, triglycerides and total cholesterol comparison with control group. Generally, the gradual improvement in blood values was noticed with the increase in concentration alcoholic extract of propolis and it had a potent antihyperglycemic effect, antioxidant activities, radical-scavenging capacities properties and that may be due to the high biological activity and nutritive values contents in bee propolis. In conclusion, the results suggest that propolis could potentially contribute for the prevention and treatment of diabetes mellitus. In conclusion, the results suggest that propolis extract has antihyperglycemic effect and could ameliorate the biochemical disturbances in diabetic rabbits.

Key-Words: Propolis, Diabetes mellitus, Biochemical parameters, Rabbits

Introduction

The term diabetes mellitus describes a metabolic disorder of multiple aetiology characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both (WHO, 1999). Diabetes mellitus is classified into four broad categories: type 1, type 2, gestational diabetes and other specific types (Shoback, 2011). The chronic hyperglycemia of diabetes is associated with damage, dysfunction and failure of various organs over the long term (Mohammadi & Naik, 2008). Diabetes is associated with the generation of reactive oxygen species (ROS), which cause oxidative damage, particularly to heart, kidney, eyes, nerves, liver, small and large blood vessels, immunological and gastrointestinal system (Obrosova *et al.*, 2003). Alloxan and streptozotocin are widely used to induce experimental diabetes in animals (Szkudelski, 2001).

In addition, alloxan has been widely used to produce experimental diabetes in animals such as rabbits, rats, mice and dogs with different grades of disease severity by varying the dose of alloxan used (Iranloye *et al.*, 2011).

Propolis is a resinous material collected by bees from buds and plant exudates which is mixed with products of their salivary glands and wax (Sforcin, 2007). Propolis contains approximately 50% resin and vegetable balsam, 30% wax, 10% essential and aromatic oils, 5% pollen, and 5% other substances as minerals and vitamins (Cohen *et al.*, 2004). Currently, more than 300 compounds, such as phenolic acid, terpenes, cinnamic acid, caffeic acid, several esters, and flavonoids have been identified as constituents of propolis from different geographic origins (Paulino *et al.*, 2003; Senedese *et al.*, 2008). The chemical composition of propolis is qualitatively and quantitatively variable, depending on the vegetation at the site from which it was collected and the time of collection (Lotti *et al.*, 2010). Chemical analysis showed availability of ten important bioactive compounds in Iraqi propolis: Flavanone, 3-Hydroxyflavone, Chrysin, Quercetin, Galangin, Apigenin, Kaempferol, O-

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coumaric acid, Caffeic acid and Ferulic acid (Ali *et al.*, 2012). In addition, propolis was extensively used to improve health and prevent diseases such as diabetes, atherosclerosis, heart diseases and cancer (Sforcin, 2007).

The present research was designed to evaluate the Iraqi propolis action on diabetic rabbits and determined some biochemical disturbances that occur after alloxan-induced diabetes.

Material and Methods

Propolis sample

The Iraqi propolis sample was obtained from beekeeper market in An- Najaf province during the year 2013. Propolis samples were kept in a dry place and stored at 4 °C until its processing.

Extraction of propolis

The Iraqi propolis sample (100 g) was cut into small pieces, and mixed with 900 ml of 70% ethanol in a volumetric flask, in the absence of bright light, with moderate shaking, at room temperature (Krell, 1996). After a week, the mixture was stirred at magnetic stirrer and filtered by filter paper (Whatman NO. 1). Then, the extract was evaporated to dryness using a freeze dryer. The yellow-brown powder of propolis was stored under sterile conditions.

Experimental animals

Adult female local rabbits *Oryctolagus cuniculus* diabetic rabbit were obtained from local market of An-Najaf, were used for the study. The experimental animals were kept at Faculty of Veterinary Medicine / University of Kufa-Iraq. All animal weights were between 1230 to 1540 gm and fed on a standard laboratory pellets and water *ad libitum*. This study was approved by the ethical committee (Department of Biology, Faculty of science /University of Kufa in 2013).

Induction of diabetes in rabbits

Diabetes mellitus was induced in rabbits after fasting of the animals for 16 hr. by a single intravenously injection of alloxan 150 mg/kg body weight which dissolved in physiological saline (0.9% NaCl) via the marginal ear vein over a period of 2 minutes. (Khushk *et al.*, 2010). The control group was injected with the same volume of isotonic saline. To prevent hypoglycemic shock and mortalities during hypoglycemic phase, the food was offered to animals immediately after alloxan injection. Besides, oral solution of 5% glucose in tap water was provided via water bottle for next 24 hr. After three days of the alloxan injection, diabetes mellitus was confirmed by the demonstration of hyperglycemia (Blood glucose >200 mg/dl). According to Schiller and McNamara (1999) animals with glucose levels over 170 mg/dl but

less than 400 mg/dl were classified as hyperglycemic. The fasting blood sugar of rabbits was estimated by glucometer (Accu- Chek active Germany) using commercially available reagent strips. The measurement of glucose level was confirmed by examining the blood taken from marginal ear vein.

Experimental design

Animals of this study were divided into five groups (each of 6) were randomly divided; the negative control group, positive control group, and three diabetic treatment groups. All rabbits except normal control were injected with alloxan monohydrate, concentration 150 mg/kg body weight. Diabetic control group did not treat with propolis. The treated animals were subdivided into three groups according to the concentration of propolis. Three oral concentrations of propolis extract were investigated (50, 100 and 200 mg/kg/day). The doses of propolis, orally 1 ml per day by syringe, were continued for 23 days.

Biochemical analysis

Which made using serum samples from both control and experimental groups. The blood was placed in tubes without anticoagulant and left at room temperature for 30 minutes for clotting, centrifuged 3000 rpm for 15 minutes. The serum was separated and transferred into Eppendorf tubes and stored at -20 °C until the measurement of the serum blood. Plasma samples were analyzed for glucose, total protein, triglycerides and total cholesterol. Colorimetric determinations were performed using spectrophotometer (Biosystems BTS-302 Spain). The absorbency was detected at an appropriate wavelength ranging from 340 to 546 nm according to the parameter tested. Basis of the tests and procedures steps are outlined by the kits suppliers. The leaflet attached with the kit describes steps of analysis.

Statistical analysis

Analysis of data was performed by using Statistical Package for the Social Sciences (SPSS-version 17). The results were expressed as (mean ± standard error). One way analysis of variance (ANOVA) followed by least significant difference (LSD) was used for the statistical comparison between control and various treated groups. Statistical significance was accepted at the $P \leq 0.05$ values. (El-Sayed *et al.*, 2009).

Results and Discussion

The results of this study showed that alloxan at concentration of 150 mg/ kg IV successfully causes diabetes in rabbits. Blood glucose level was strongly elevated on the second day after treatment (Table 1). The findings of this study showed a significant increase ($P < 0.05$) in fasting blood glucose in diabetic rabbits when compared with normal control rabbits. In

contrast, administration of propolis to diabetic rabbits resulted in a significant decrease ($P < 0.05$) in glucose levels compare with diabetic group throughout the experiment.

The results in table (1) revealed a marked decrease ($P < 0.05$) in the total protein levels of alloxan-injected rabbits in comparing with control group. Administration of ethanolic extract of propolis (EEP) to diabetic rabbits at concentrations 50,100 and 200mg/kg resulted in significant increases ($p < 0.05$) in total protein levels when compared with diabetic group. At the same time, Triglyceride and total cholesterol values increased significantly ($P < 0.05$) in diabetic rabbits as compared to the control group. Treatment with the ethanolic extract of propolis (EEP) significantly ($P < 0.05$) decreased the triglycerides and cholesterol values in the diabetic rabbits.

The results in Table (2) indicate significant differences ($P < 0.05$) in the body and liver weights of alloxan-induced diabetic rabbits in comparing with normal control groups. Treatment of the diabetic rabbits with (EEP) at concentration 200mg/kg showed significant increase ($p < 0.05$) in body weight when compared with diabetic group, but no significant difference in body weight in comparison with control group. The effect of (EEP) on liver weight of rabbits with alloxan-induced diabetes is shown in Table (2). The results revealed a significant increase ($P < 0.05$) in the liver weight of alloxan-induced diabetic rabbits (3.88%) in comparing with control group (3.20%). Treatment of the diabetic rabbits with (EEP) at concentration 50, 100 and 200mg/kg of body weight showed significant decrease ($p < 0.05$) in the liver weight ratio (3.14, 3.20, 3.11 %) respectively in comparison with diabetic rabbits (3.88%).

Table (1): Effect of propolis extract on biochemical parameters of diabetic rabbits

Groups Parameters	C	D	P50	P100	P200
Glucose mg/dl	113.75 ± 5.26	372.50 ^a ±10.12	262.75 ^{a,b} ±3.35	254.50 ^{a,b} ±5.37	144.5 ^{a,b,c,d} ± 7.30
Total protein g/dl	6.8 ± 0.34	4.2 ^a ±0.39	5.2 ^{a,b} ±0.08	7.5 ^{b,c} ±0.39	8.0 ^{a,b,c} ± 0.35
TG mg/dl	55.5 ±2.1	176.5 ^a ± 8.65	110.0 ^{a,b} ± 5.4	740.0 ^{a,b,c} ±2.91	68.2 ^{b,c} ± 2.09
TC mg/dl	103.00 ±7.85	244.50 ^a ±14.7	155.00 ^{a,b} ±7.49	121.75 ^{b,c} ± 5.36	109.50 ^{b,c} ±1.93

- C: control group, D: diabetic group, P: propolis-treated groups.

- Data are expressed as mean ± standard error.

- Significant differences between groups are indicated with different letters.

* Significant difference at ($P < 0.05$).

The alloxan monohydrate is one of the chemical agents used to induce diabetes mellitus. It induces diabetes by partial destruction of the β -cells of islets of Langerhans (Szkudelski, 2001). Alloxan is selectively taken up into the β -cells by a glucose transporter (GLUT2) (Munday *et al.*, 1993) and GLUT2 has been recognized as a target molecule for alloxan (Schulte *et al.*, 2002). Hyperglycemia occurs because the liver and skeletal muscle cannot store glycogen and the tissues are unable to take up and utilize glucose (Lamba *et al.*, 2000). In this study, the mechanism effect of Iraqi propolis extract in lowering blood sugar has been

studied. The significant antihyperglycemic effect of propolis is probably due to its flavonoid contents. Also saponins role in decrease blood sugar by ways stimulate β -cells (Kubo *et al.*, 2000). Our results are in line with data reported by others. Wang and Li (2004) suggest that the (EEP) has a beneficial effect on reduction of blood sugar levels in alloxan-induced diabetes mice. Also, it has been reported that the water extract of propolis (200 mg/kg) prevented β -cells destruction by inhibiting IL- β generation and NO synthase activity (Matsushige *et al.*, 1996).

Table (2): Effect of propolis extract on the body and liver weights of diabetic rabbits

Groups	Body weight (gm)			LW/100 g BW
	Initial weight	Final weight	Increase	
C	1641.25	1903.75	262.50 ± 15.61	3.20 ± 0.22
D	1336.25	1460.00	123.75 ± 9.43 ^a	3.88 ± 0.07 ^a
P50	1512.50	1636.25	123.75 ± 2.39 ^a	3.14 ± 0.10 ^b
P100	1542.50	1668.75	126.25 ± 5.90 ^a	3.20 ± 0.02 ^b
P200	1408.75	1641.25	232.50 ± 17.85 ^{b,c,d}	3.11 ± 0.07 ^b

- C: control group, D: diabetic group, P: propolis-treated groups.

- Data are expressed as mean ± standard error.

- Significant differences between groups are indicated with different letters.

* Significant difference at (P<0.05).

The findings of this study revealed there were marked decrease in serum level of total protein in alloxan-induced diabetic rabbits and this is in accordance with results that demonstrated by Kumar *et al.* (2011) in rats and Oršolić *et al.* (2012) in mice. The recent literature suggests that the decrease in protein due to free radicals that caused liver cells damage and this leading to decrease in protein synthesis (Romero & Strick, 1993). Also, insulin deficiency leads to various metabolic aberrations in the animals such as decreased protein content. Insulin deficiency causes excessive catabolism of protein, and the amino acid released are used for gluconeogenesis (kumara & Devi, 1998).

Pathak and Dhawan, (1988) reported that renal disease is one of the most common and severe complications of diabetes. Insulin is a physiological factor, which plays an important role in the maintenance of protein balance, since it not only stimulates the uptake of amino acids and protein synthesis, but also inhibits protein degradation.

Total protein reached the normal level in the group treated with the intermediate dose of propolis (100 mg/kg) when compare with control group and the untreated diabetic rabbits. This could be due to a better

control the glucose level and protein release during treatment. In addition, propolis may prevent hepatorenal injury by inhibiting lipid peroxidation and enhancing the activities of antioxidant enzymes (Abo-Salem *et al.*, 2009). Hypertriglyceridemia and hypercholesterolemia have been reported to occur in alloxan-induced diabetic rabbits (Wojtowiczet *et al.*, 2004) and a significant increase observed in our experiments was in accordance with those studies. Elevation of glucose and decline of insulin cause decrease in lipoprotein lipase (LPL) in adipose tissue, and this lead to accumulate of triglycerides as energy source (Kovar *et al.*, 2004). The results obtained from the present study show that administration of propolis at different concentrations significantly improved triglycerides and total cholesterol levels in a dose-dependent manner. Moreover, the highest concentration of propolis (200 mg/kg) was able to reduce levels to the normal range.

The results of our study coincide with the findings Abo-Salem *et al.* (2009) who show propolis reduces level of triglycerides in the blood of diabetic animals, and corroborated previous studies that demonstrated the regulation of lipid metabolism by propolis from different sources (Nader *et al.*, 2010).

The finding of this study also showed that significant differences ($P < 0.05$) in the body and liver weights of alloxan-induced diabetic rabbits. This result was expected because it's well known that diabetes causes decrease in the whole body weight which considers one of the most important diagnostic symptoms of diabetes (ADA, 2011). Also, insulin is a potent anabolic hormone which promotes the synthesis and storage of carbohydrates, lipids and proteins (through increasing the uptake of glucose, amino acids and fatty acids into cells, and increases the expression and the activity of enzymes that catalyze glycogen, lipid and protein synthesis), and inhibiting their degradation and release into the circulation (Chang *et al.*, 2004). So the decrease of insulin sensitivity in diabetic animals may be one of the causative factors of weight loss.

Results of this study demonstrated that (EEP) only at concentration 200 mg/kg resulted in marked increase in animal body weight when compared to the diabetic group. Propolis treatment significantly improved the body weight of diabetic rats. Improved body weight of diabetic rabbits treated with (EEP) could be due to a better control of hyperglycemic state compared to the untreated diabetic animals. Besides, it has been suggested that bee propolis contain protein, amino acids, vitamins and flavonoids. For this reason, some people use propolis as a general nutritional supplement (Lee *et al.*, 2001).

The significant increase in liver weight in our study may be due to the elevated fats content. Using the techniques of magnetic resonance image (MRI) to measure liver size and fat content, a study had clearly demonstrated that a large proportion of excess liver size is attributable to liver fat content (Lewis *et al.*, 2006). These results agree with the results that obtained by Zhu *et al.* (2011) who study the effect of Chinese propolis and Brazilian propolis on streptozotocin-induced type 1 diabetes mellitus in rats.

The enhancement in liver weight may reflect the ability of propolis to repair the defect which causes the weight change. It is reported that the presence of phenolics and dicaffeoylquinic acid derivatives and flavonoids are known to have a hepatoprotective function. Hepatoprotective activity for different types of propolis has been reported, which correlated to the antioxidant activity (Banskota *et al.*, 2001). According to Ozen *et al.* (2004) and Nirala *et al.* (2008) there is decrease in the liver weight due to propolis and its active constituent caffeic acid phenethyl ester which have apparent therapeutic effects on liver lesions in animal models.

In conclusions this study revealed that ethanolic extract of propolis possesses antihyperglycemic property as well as improves body weight, liver weight, total protein, lipid profile in Alloxan-diabetic rabbits as well as, ethanolic extract of propolis at 200 mg/kg of body weight would be safer and useful in treating diabetes mellitus in rabbits and has demonstrated greater protection against oxidative stress. The author recommends future studies on propolis that explore the chemical compounds responsible for the antihyperglycemic effect.

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