Bahathiq, Prensa Med Argent 2018, 104:6
DOI: 10.41720032-745X.1000322

La Prensa Medica Argentina

Research Article A SCITECHNOL JOURNAL

Assessment the Potential Effects of Propolis Water Extract in Stz-Diabetic Rats

Adil Omar Bahathiq*

Abstract

The present study was designed to investigate the probable hypoglycemic, hypolipidemic and hepatoprotective effects of propolis water extract in diabetic rats. Diabetes was induced in male rats by intraperitoneal injection of single dose (45 mg/kg body weight) of streptozotocin (STZ). After induction of diabetes, rats were orally administered propolis in two separate doses, 50 or 100 mg/kg body weight daily for 6 weeks. Herein, propolis administration significantly improve the hyperglycemic status resulting from diabetes induction, as evidenced by lowered blood glucose, blood glycosylated hemoglobin levels and hepatic G-6-Pase activity, while enhanced serum insulin, blood hemoglobin levels and hepatic glycogen content, compared to the diabetic group. Regarding lipid metabolism, the increased levels of lipid fractions, and the reduced high density lipoprotein cholesterol level in diabetic rats were reverted back to normal levels after propolis administration indicating, further, its hypolipidemic effect. Moreover, propolis enhanced the body weight gain and protein metabolism in diabetic rats. In addition, propolis was found to has hepatoprotective effects via improving liver functions in diabetic rats, which was confirmed by decreased serum AST, ALT and γ-GT activities associated with decreased bilirubin level, compared to the diabetic group. Current findings clearly point out the antidiabetic, hypolipidemic and hepatoprotective properties of propolis water extract which may be of health benefits in ameliorating various metabolic disorders and complications of diabetes.

Keywords

Diabetes; Streptozotocin; Propolis; Hypoglycemia; Hyperlipidemia; Protein metabolism; Liver functions

Introduction

Diabetes mellitus (DM) is a major endocrine disorder, affecting approximately 5% of the world's population [1]. DM, a global health crisis, is one of the most common non-communicable diseases affecting humanity regardless of the geographic location or socioeconomic profile of the population [2], rising to epidemic proportions globally and undoubtedly one of the major challenging public health problems in the twenty-first century as it considered the principle cause of great economic loss that can impede nation's development [3], as It considered one of the five leading causes of death in world [4]. It is a chronic metabolic disorder that characterized by elevated blood glucose levels with carbohydrate, protein, and fat metabolism disturbances which result, in part, from absolute or relative deficiency of insulin (type I and type II, respectively). Chronic hyperglycemia considered the main risk factor in both types for the development of diabetic complications as it is thought that frequent or large glucose fluctuations may independently contribute to the development of these complications [5]. Experimentally, STZ has been found to produce a selective toxic effect on β-cells and induces DM type I in most laboratory animal species [2]. STZ Type I DM is induced by pancreatic β-cells destruction with eventual absence of insulin, mediated by an autoimmune mechanism and consequent inflammatory process through production of many inflammatory cytokines (TNF-α, IFN-γ and IL-1β) and oxidative stress markers [6]. In diabetics, depending on the severity of the diabetes, higher level blood glucose will be reached and remain increased for long duration, through hepatic glucose overproduction and peripheral underutilization. Gailliot et al. [7], Singh and Kakkar [8] reported that STZ treated rats showed a significant elevation in serum glucose levels, while a marked decrease in serum insulin levels were observed. This is in accordance with who found hyperglycemia and glucose intolerance with marked decrease in serum insulin levels in STZ-diabetic rats. Similar results obtained in STZ induced type II diabetic mice by Manjusha et al. [9], who found a marked increase of FBG levels accompanied by marked decline in serum insulin levels. Glycogen is the body auxiliary energy source that trapped and converted back into glucose by glucose-6-phosphatase (G-6-pase) enzyme when there is need for energy. In experimental diabetes, enzymes responsible for glucose and fatty acids metabolism are markedly altered [10]. G-6-pase activity was significantly increased while glycogen synthesis was decreased in the liver of STZ-diabetic rats [11]. Similar results obtained by Xie et al. [12]. who reported that injection of rats with STZ resulted in significant decline in glycogen contents with marked elevation in G-6-pase activity in their livers. In diabetes, since various proteins, such as hemoglobin (Hb), undergo non-enzymatic glycation, blood excess glucose can bind with Hb forming glycosylated hemoglobin (HbA1c) [13]. Hb content was significantly decreased, while HbA1c level was elevated in STZ-induced diabetic rats [14]. Such results were in accordance with the results revealed a significant increase in HbA1c level associated with Hb level decline in diabetic patients [15] and rats [16]. Diabetes is associated with profound alterations in the lipoprotein profile and plasma lipids with increasing risk of, coronary insufficiency, myocardial infarction and atherosclerosis [17]. Disturbance in lipid metabolism is so prominent that diabetes has been called "more a disease of lipid than carbohydrate metabolism". Because, glucose cannot be used effectively as a metabolic fuel, the mobilization of energy reserves from fat stores is enhanced, leading to elevated concentration of fatty acids, glycerol and ketones in the blood [18]. Over 95% of all lipids transported in the blood are present in lipid-protein or lipoprotein and such types were affected vigorously in diabetes. A significant increase in serum total cholesterol (TC), triglycerides (TG), total lipids (TL), low density lipoprotein-cholesterol (LDL-C) and very low density lipoprotein-cholesterol (VLDL-C)

***Corresponding author:** Adil Omar Bahathiq, Department of Physiology, Faculty of Medicine, Um-Alqura University, Saudi Arabia, Tel: +966 12 550 1068, E-mail: drbahtihiq@hotmail.com

Received: July 09, 2018 **Accepted:** November 30, 2018 **Published:** May 06, 2018

doi: 10.41720032-745x.1000322

along with a decrease in serum high density lipoprotein-cholesterol (HDL-C) levels were observed in STZ diabetic rats [8,16,19] as well as in diabetic patients [20]. An association between diabetes mellitus and deranged protein metabolism has been known for many years ago. The decrease in serum and hepatic total proteins in diabetic patients may be due to microproteinuria and/or increased protein catabolism since insulin inhibits hepatic amino acid release [21]. Several reports showed that serum total proteins, globulin and albumin levels were markedly lowered in STZ-diabetic rats [9,8]. STZ injection induces hepatocellular damage, which is one of the characteristic changes in diabetes [2]. The elevated serum glucose level, aspartate transaminase (AST), alanine transaminase (ALT), and γ-GT, among various biochemical parameters, were found to be indicative of liver damage, hepatic functions change, cellular leakage and loss of functional integrity of hepatic cell membranes [22]. These enzymes release into the serum is a result of changes in the permeability of liver membranes and/or tissue injury. Oche et al. [2], Xie et al. [12] and Arya et al. [23] reported that in STZ diabetic rats there was a marked increase in serum AST, ALT and γ-GT due to damage occurred in the liver tissue as a result of hyperglycemia. Bilirubin is excreted by liver; therefore, interference with the normal liver functions affects its rate of conjugation and excretion. Thus a high level of bilirubin is used as indices for liver function and bile excretion status. Diabetes was found to increase the plasma total bilirubin, through decreasing its liver uptake and conjugation or increasing its production from RBCs hemolysis, indicating presence of liver problems [2]. Although, effective control of blood glucose level is an effective strategy in reducing clinical complications of DM remarkably, optimal control of blood glucose level alone could not prevent complications which promote to hypothesize an alternative treatment approaches essentiality. Even though there is no cure for diabetes, the pharmacological and non-pharmacological approaches certainly improved the prognosis and improved the quality of life to certain extent [24]. In recent years, studies are increasing in the field of free radical induced oxidative damage in human diseases including diabetes. Various antioxidants, vitamins and other natural products are being investigated to encounter oxidative events. Thus, identification of naturally occurring inhibitors of peroxidation to be taken in diet can lead to important strategies for disease prevention. Diabetes management without any side effects is a huge challenge leading to increase demand for natural products as a preventive agent for diabetes treatment that possess antidiabetic activity with fewer side effects. In recent years, bees-derived natural products received considerable attention because of their diverse pharmacological actions. Realizing this fact, propolis was taken into account as a natural product for its emerging hypoglycemic and antioxidant efficacy [25]. Propolis (bee glue) is a complex resinous substance collected by honeybees, especially *Apis mellifera*, from a variety of plant sources including cracks in bark and leaf buds. It is a strong adhesive material used by bees in the construction, maintenance, and protection of their hives. It has a complex chemical composition and is known to be rich in polyphenols, flavonoids, waxes, resins, balsams, amino acids, oils, etc [26]. In many countries, it has been used in folk medicine since ancient times and recently, it was reported to possess multiple biological activities, such as antifungal, antibacterial, antiviral, antioxidant, anticancer, immunomodulatory, wound healing, hepatoprotective and anti-inflammatory [27]. Thus, it has been extensively used in beverages and food to improve health and prevent diseases such as heart disease, inflammation, cancer and diabetes [28]. The results of previous experiments were highly encouraging as they revealed that propolis administration significantly lower the level of blood glucose in STZ – induced diabetic rats and in glucose load condition, as it can protect pancreatic tissue by enhancing the antioxidant defense system with its hypoglycemic and hypolipidemic activities, which can be used to delay or prevent diabetic complications [29]. Similar results were obtained by Al-Hariri et al. [29] and Lio et al. [30] who showed that oral administration of encapsulated propolis can control hyperglycemia as it can significantly inhibit FBG elevation and improve insulin sensitivity in STZ-diabetic rats. These results are in agreement with the findings of Bhadauria et al. [31] who found that 3 weeks propolis treatment (200 mg/kg b.w) raise hepatic glycogen store in diabetic rats accompanied with a significant decrease in G-6-pase activity. For lipid metabolism, Fuliang et al. [32] observed that 7 weeks propolis ethanolic or water extract (150 mg/kg bw) oral administration may modulate lipid metabolism, in STZ-diabetic rats, as propolis significantly lowered serum TC (20.4%), TG (36.8%), LDL-c (46.3%) levels and increased serum HDL-c (11.1%) levels. Similar results were obtained by Al-Hariri [25] and Lio et al. [30]. Regarding protein metabolism, Yonar et al. [33] reported that treatment of diabetic rats with propolis water extract resulted in a significant increase in serum total proteins, albumin and globulins as compared with the diabetic group. The results are in harmony with the findings of El-Sayed et al. [34] who reported that oral treatment of STZ-induced diabetic rats with 200 mg/kg bw of propolis for 5 weeks ameliorated alterations in serum total proteins. Concerning liver damage, Bhadauria et al. [35] concluded that propolis extract possesses therapeutic potential against hepatic damage. This is confirmed by Zhu et al. [36] who posted that long-term administration of water propolis extract (200 mg/kg bw) resulted in marked improvement of the liver lesions in STZ-diabetic rats where serum AST and ALT levels were significantly decreased. Moreover, El-sharaky et al. [37] showed that propolis reduced the increased levels of AST and ALT in plasma of the diabetic rats. All of this suggests that propolis water extract may has potential as a pharmaceutical for patients suffering from various diseases such as cardiovascular diseases, cancer, and diabetes [38]. Therefore, the target of the present research is the examination of the overall action of propolis as natural substance that can be used in curing diabetic complications.

Materials and Methods

Chemicals

STZ was purchased from Sigma Aldrich Co. (St. Louis, Mo 6, USA). Bio propolis capsules were purchased from Egyptian Sigma Pharmaceutical Industries Company, Egypt.

Animals

Adult male albino rats (*Rattus rattus*), weighing 100-120 g, were kept under a photoperiod of 12 h light: 12 h darkness, with lights-on from 06.00 to 18.00 h. They housed in stainless cages in a good-ventilated animal room. Rats were fed on adequate stable diet and water were allowed *ad libitum*. After a week of acclimatization, the rats were divided into six groups each of six animals.

Induction of diabetes

Overnight fasting rats were injected intraperitoneally with a single dose of freshly prepared STZ solution (45 mg/kg body weight) dissolved in citrate buffer, pH 4.6. Two days after induction, diabetes was confirmed by examining blood glucose level using Glukotest of diagnosis glucose level by ACCU–CHEKGo apparatus obtained from Roche Company, Germany [13]. Rats with fasting blood glucose level over 200 mg/dl are considered as diabetic rats [39].

doi: 10.41720032-745x.1000322

Experimental design

The rats were divided into six groups of 6 each: the first group served as control and had no treatment; the second group received propolis in a dose of 50 mg/kg body weight; the third group received propolis in a dose of 100 mg/kg body weight; the fourth group injected intraperitoneally with a single dose of STZ solution, 45 mg/kg body weight (diabetic group); the fifth group was diabetic and received propolis in a dose of 50 mg/kg body weight; the sixth group is diabetic and received propolis in a dose of 100 mg/kg body weight. After the induction of diabetes, all rats, except the control, were orally administered the selective doses of propolis daily for 6 weeks period.

Samples collection

At the end of the experimental period, overnight fasted rats were weighed then sacrificed by cervical decapitation using a sharp razor blade. Blood samples were collected in clean centrifuge tubes, and let stand for appropriate time, after which they were centrifuged at 3000 rpm for 15 min. Blood sera were carefully separated, labeled and kept at -20°C for selective biochemical analysis. On the other hand, liver and pancreas specimens were quickly removed from the animals, weighed, homogenized in distilled water, labeled and kept together with sera at -20°C until furtherassays.

Biochemical determinations

Fasting serum glucose, hemoglobin and serum HDL-C concentration were estimated by the methods of Trinder [40], Van and Zijlstra [41] and Grove, respectively using SPINREACT diagnostics kit, Spain. Meanwhile, glycosylated hemoglobin was estimated according to the method of Gonen and Rubenstein [42] by using glycosylated hemoglobin kit obtained from Teco Diagnostics, U.S.A. Serum insulin was measured by ELISA kit purchased from Boehringer Mannheim, Germany, according to the method of Flier et al. [43] using Boehringer Analyzer ES 300. Liver glycogen content and glucose-6-phosphatase activity were determined as described by Damsbo et al. [44] and Rossetti et al. [45] methods, respectively. Serum LDL-C and globulins levels were calculated according to Friedewald, [46] and Young [47] equations, respectively. Serum and hepatic total cholesterol, triglycerides, total lipids and total proteins were estimated using kits from Biodiagnostic Company, Egypt according to Young [47], Fossati and Prencipe [48], Zollner and Kirsch [49], Henry methods, respectively, while serum albumin level was estimated by colorimetric method of Young [47] using albumin –kit from Diamond Company, Egypt. Using kits from ELITech Company, France, serum AST, ALT and γ-GT activities were estimated by the methods of Scherwin et al. [50] Serum total bilirubin content was detected according to Young [47] using total bilirubin–kit from Diamond Company, Egypt.

Statistical analysis

Obtained data were statistically evaluated with SPSS 17.5 software. *P* values equal or less than 0.05 were considered the minimal level of significance. All the results were expressed as the mean ± SE for six animals in each group. Percentage of change in the treated groups was calculated.

Results

Table 1 shows serum glucose and insulin levels, hepatic glycogen content and G-6-Pase activity, and blood Hb level and HbA1C (%). The results showed that daily administration of low or high doses of propolis water extract for 6 weeks produced no significant change in all tested parameters concentration when compared to the control group. In STZ-diabetic groups, significant increases in glucose, G-6-Pase and HbA1C levels, while significant decrease in insulin, glycogen and Hb concentrations, were obtained comparing with control results. Diabetic rats treated with propolis showed marked decreases in glucose, G-6-Pase and HbA1C levels, while significant increase in insulin, glycogen and Hb concentrations when compared to the diabetic group. Although this, the results of glucose (in case of low propolis dose) and G-6-Pase appeared significantly high, where glycogen contents appeared significantly low in comparison with control groups. There were no remarkable changes between the

Table 1: Serum glucose and insulin levels, hepatic glycogen content and G-6-Pase activity, and blood Hb level and HbA1C (%) in in different animal groups.

Parameter / Group		Control	Propolis (P)		Diabetic (D)	D + P	
			Low	High		Low	High
Glucose (mg/ 100 ml)	Mean ± SE	100.71 ± 7.71	100.60 ± 7.57	100.17 ± 4.10	324.35 ± 24.57[a]	124.73 ± 15.43[b]	145.03 ± 12.61[a,b]
	*		- 0.10	- 0.53	+ 222.06	+ 23.85	+ 44.00
	**					- 61.54	- 55.28
Insulin (µ l U/ml)	Mean ± SE	22.80 ± 1.32	21.79 ± 1.24	21.80 ± 1.56	14.57 ± 0.82[a]	22.76 ± 0.87[b]	23.34 ± 1.72[b]
	*		- 4.42	- 4.38	- 36.09	- 0.17	+ 2.36
	**					+ 56.21	+ 60.19
Glycogen (g/100 g)	Mean ± SE	44.44 ± 0.78	43.50 ± 0.73	42.23 ± 1.12	31.08 ± 0.36[a]	40.65 ± 0.61[a,b]	40.76 ± 0.90[a,b]
	*		- 2.11	- 4.97	- 30.06	- 8.52	- 8.28
	**					+ 30.79	+ 31.14
G-6-Pase (µ mol Pi/ min/g)	Mean ± SE	2.42 ± 0.19	2.38 ± 0.19	2.32 ± 0.06	3.25 ± 0.19[a]	2.80 ± 0.01[a,b]	2.76 ± 0.13[a,b]
	*		- 1.65	- 4.13	+ 34.29	+ 15.70	+ 14.04
	**					- 13.84	- 15.07
Hb (g/dl)	Mean ± SE	13.41 ± 0. 25	12.98 ± 0.40	12.96 ± 0.28	9.37 ± 0.29[a]	13.05 ± 0.27[b]	13.57 ± 0.24[b]
	*		- 3.20	- 3.35	- 30.12	- 2.68	+ 1.19
	**					+ 39.27	+ 44.82
HbA1C (%)	Mean ± SE	3.36 ± 0.19	3.34 ± 0.25	3.03 ± 0.15	5.73 ± 0.16[a]	3.67 ± 0.39[b]	4.32 ± 0.54[b]
	*		- 0.59	- 9.82	+ 70.53	+ 9.22	+ 28.57
	**					- 35.95	- 24.60

Values expressed as mean ± SE (n = 6); a, b Significant difference (P ≤ 0.05) comparing to control and diabetic groups respectively; * , ** are % of changes comparing to control and diabetic groups respectively.

doi: 10.41720032-745x.1000322

results of low and high doses of propolis in STZ-diabetic rats. The data of serum and hepatic TL, TG and TC levels were summarized in Table 2**.** Daily administration propolis in low and high doses for 6 weeks induced no marked alterations in all mentioned parameters, when compared to control values. However, diabetic groups displayed significantly increased these variables, comparing with control results. Administration of both low and high doses of propolis partially ameliorated the adverse effect of STZ diabetes since obtained data showed significant decreases in all tested parameters when compared to the diabetic group, except the low dose propolis treated group in case of hepatic TC which showed no significant change. In comparison with control groups, levels of serum TG and TC in diabetic rats treated with low and high doses of propolis and hepatic TC content in diabetic rats treated with low dose of propolis were still significantly elevated, while levels of remaining data appeared unchanged. Obtained results displayed non-significant changes between low and high doses of propolis in STZ-diabetic rats. Serum levels of HDL-C, LDL-C and HDL/LDL ratio were demonstrated in Table 3. Obtained results showed that daily administration of low or high dose of propolis extract for 6 weeks resulted in non significant changes, when compared to the control groups. Remarkable significant increases in tested parameters were seen in diabetic groups, when compared to the control groups. The results also exhibited significant increases in HDL-C level and HDL/LDL ratio associated with a significant decrease in LDL-C level in STZ-diabetic rats treated with low and high doses of propolis, comparing with diabetic groups. Although LDL-C levels still significantly higher and HDL/LDL ratio still significantly lower, when compared to control groups. No detectable changes were recorded between low and high doses of propolis in STZ-diabetic rats except in case of LDL-C where it showed in a significant decrease.

Table 4 illustrates Hepatic total proteins content and serum total proteins, albumin and globulins levels. Following daily administration of low and high doses of propolis water extract for 6 weeks, obtained results showed no significant changes in all tested parameters, when compared to control group. However, in STZ-diabetic groups, significant decreases were noted, comparing with control results. Following treatment with propolis in STZ-diabetic rats, significant rise in all tested parameters were detected, comparing with results obtained from diabetic rats. In comparison with control groups,

Table 2: Serum and hepatic TL, TG and TC levels in different animal groups.

Parameter / Group		Control	Propolis (P)		Diabetic (D)	D + P	
			Low	High		Low	High
Glucose (mg/ 100 ml)	Mean ± SE	256.67 ± 20.90	282.93 ± 16.66	276.34 ± 14.99	502.29 ± 27.43[a]	286.66 ± 14.56[b]	283.90 ± 10.92[b]
	*		+ 10.23	+ 7.66	+ 95.69	+ 11.68	+ 10.60
	**					- 42.92	- 43.47
Insulin (µ l U/ml)	Mean ± SE	330.26 ± 27.16	338.53 ± 34.87	321.07 ± 32.93	581.79 ± 42.57[a]	369.11 ± 45.70[b]	353.85 ± 41.73[b]
	*		+ 2.50	- 2.78	+ 76.16	+ 11.76	+ 7.14
	**					- 36.55	- 39.17
Glycogen (g/100 g)	Mean ± SE	50.18 ± 0.47	53.38 ± 0.37	52.74 ± 0.36	109.57 ± 0.44[a]	65.47 ± 0.33[a,b]	64.74 ± 0.43[a,b]
	*		+ 6.37	+ 5.10	+ 118.35	+ 30.47	+ 29.01
	**					- 40.24	- 40.91
G-6-Pase (µ mol Pi/ min/g)	Mean ± SE	52.61 ± 4.15	57.71 ± 5.53	55.35 ± 5.07	106.96 ± 8.65[a]	64.18 ± 5.18[b]	67.56 ± 6.52[b]
	*		+ 9.69	+ 5.20	+ 103.30	+ 21.99	+ 28.41
	**					- 39.99	- 36.83
Hb (g/dl)	Mean ± SE	90.86 ± 0.81	92.25 ± 0.72	92.99 ± 0.65	139.59 ± 0.34[a]	109.78 ± 0.49[a,b]	109.12 ± 0.72[a,b]
	*		+ 5.93	+ 2.34	+ 53.63	+ 20.82	+ 20.09
	**					- 21.35	- 21.82
HbA1C (%)	Mean ± SE	145.13 ± 5.82	160.92 ± 6.53	147.44 ± 4.50	203.20 ± 15.09[a]	174.73 ± 9.37[a]	151.26 ± 4.64[b]
	*		+10.87	+ 1.59	+ 40.01	+ 20.39	+ 4.22
	**					- 14.02	- 25.56

Values expressed as mean ± SE (n=6); a, b Significant difference (P ≤ 0.05) comparing to control and diabetic groups respectively; * , ** are % of changes comparing to control and diabetic groups respectively.

Table 3: Serum HDL-C, LDL-C and HDL/LDL ratio in different animal groups.

Parameter / Group		Control	Propolis (P)		Diabetic (D)	D + P	
			Low	High		Low	High
HDL-C (mg/dl)	Mean ± SE	38.42 ± 0.97	40.78 ± 0.90	39.21 ± 0.90	21.17 ± 0.67[a]	35.02 ± 1.04[b]	38.42 ± 0.67[b]
	*		+ 6.14	+ 2.05	- 44.89	- 8.84	0.00
	**					+ 65.42	+ 81.48
LDL-C (mg/dl)	Mean ± SE	42.40 ± 0.45	44.96 ± 0.26	43.22 ± 0.41	96.50 ± 0.44[a]	61.63 ± 0.66[a,b]	57.69 ±1.01[a,b,c]
	*		+ 6.03	+ 1.93	+ 127.59	+ 45.35	+ 36.06
	**					- 36.13	- 40.21
HDL/LDL ratio	Mean ± SE	0.90 ± 0.03	0.90 ± 0.02	0.91 ± 0.02	0.21 ± 0.0 [a]	0.57 ± 0.02[a,b]	0.66 ± 0.02[a,b]
	*		0.00	+ 1.11	- 76.66	- 36.66	- 26.66
	**					+ 171.42	+ 214.28

Values expressed as mean ± SE (n=6); a, b, c Significant difference (P ≤ 0.05) comparing to control, diabetic and D+P low dose groups respectively; * , ** are % of changes comparing to control and diabetic groups respectively.

doi: 10.41720032-745x.1000322

Table 4: Hepatic total proteins content and serum total proteins, albumin and globulins levels in different animal groups.

Parameter / Group		Control	Propolis (P)		Diabetic (D)	D + P	
			Low	High		Low	High
Hepatic total proteins (g/100 gm)	Mean ± SE	7.17 ± 0.32	7.18 ± 0.30	7.16 ± 0.08	5.03 ± 0.19[a]	6.21 ± 0.27[a,b]	6.50 ± 0.25[b]
	*		+ 0.13	- 0.13	- 29.84	- 13.38	- 9.34
	**					+ 23.45	+ 29.22
Serum total proteins (g/dl)	Mean ± SE	5.88 ± 0.22	6.01 ± 0.61	5.80 ± 0.39	3.39 ± 0.13[a]	5.27 ± 0.25[b]	5.50 ± 0.33[b]
	*		+ 2.21	- 1.36	- 42.34	- 10.37	- 6.46
	**					+ 55.45	+ 62.24
Albumin (g/dl)	Mean ± SE	3.26 ± 0.12	3.15 ± 0.06	3.31 ± 0.06	1.54 ± 0.12[a]	2.65 ± 0.09[a,b]	2.56 ± 0.13[a,b]
	*		- 3.37	+ 1.53	- 52.76	- 18.71	- 21.47
	**					+ 72.07	+ 66.23
Globulins (g/dl)	Mean ± SE	2.48 ± 0.26	2.55 ± 0.41	2.40 ± 0.34	1.79 ± 0.17[a]	2.55 ± 0.30[b]	2.48 ± 0.34[b]
	*		+ 2.82	- 3.22	- 27.82	+ 2.82	0.01
	**					+ 42.45	+ 38.54

Values expressed as mean ± SE (n = 6); a, b Significant difference (P ≤ 0.05) comparing to control and diabetic groups respectively; * , ** are % of changes comparing to control and diabetic groups respectively.

Table 5: Serum AST, ALT and γ-GT activities and total bilirubin level in different animal groups.

Parameter / Group		Control	Propolis (P)		Diabetic (D)	D + P	
			Low	High		Low	High
AST (u/l)	Mean ± SE	75.76 ± 2.30	79.61 ± 4.66	79.00 ± 1.78	118.47 ± 2.11[a]	90.92 ± 5.68[a,b]	87.00 ± 3.98[a,b]
	*		+ 5.08	+ 4.27	+ 56.37	+ 20.01	+ 14.83
	**					- 23.25	- 26.56
ALT (u/l)	Mean ± SE	36.84 ± 2.72	43.64 ± 3.61	45.55 ± 2.44	102.95 ± 2.26[a]	56.74 ± 1.78[a,b]	52.95 ± 3.17[a,b]
	*		+ 18.45	+ 23.64	+ 179.45	+ 54.01	+ 43.72
	**					- 44.88	- 48.56
γ-GT (u/l)	Mean ± SE	32.42 ± 0.93	33.93 ± 1.25	32.97 ± 1.15	76.42 ± 2.83[a]	41.98 ± 1.26[a,b]	42.68 ± 1.05[a,b]
	*		+ 4.65	+ 1.69	+ 135.71	+ 29.48	+ 31.64
	**					- 45.06	- 44.15
Bilirubin (mg/dl)	Mean ± SE	0.85 ± 0.04	0.88 ± 0.04	0.84 ± 0.02	3.09 ± 0.08[a]	2.07 ± 0.02[a,b]	1.93 ± 0.09[a,b]
	*		+ 3.52	- 1.17	+ 263.52	+ 143.52	+ 127.05
	**					- 33.00	- 37.54

Values expressed as mean ± SE (n = 6); a, b Significant difference (P ≤ 0.05) comparing to control and diabetic groups respectively; * , ** are % of changes comparing to control and diabetic groups respectively.

significantly lowered serum albumin in diabetic rats treated with low and high doses of propolis were observed, and after low dose treatment in case of hepatic total proteins. The results reveal a non-significant change between low and high doses of propolis in diabetic rats. Table 5 represents serum AST, ALT and γ-GT activities and total bilirubin level. Results of this study sshowed that daily administration of low or high doses of propolis extract for 6 weeks showed non significant changes in all liver function markers levels when compared to the control group. Regarding to diabetic group, a significant increases were obtained when compared to normal control one. In contrary, diabetic groups treated with propolis showed significant increases in all tested parameters when compared to the diabetic group, although these values still significantly higher when compared to normal control group. A non significant change was detected between low and high doses of propolis in diabetic rats.

Discussion

Diabetes mellitus (DM) is a global health care issue resulting from hyperglycemia-mediated life-threatening complications. Although the use of glucose-lowering agents is routinely practiced, high dependence on medication leads to poor quality of life for DM patients. While it is still not feasible to precisely determine the critical timing when DM is truly established, perhaps the best way to reduce DM-associated mortality is to prevent it [51]. Though different types of oral hypoglycemic agents are available for DM treatment, increasing demand to use antidiabetic natural products were observed because of the existing drugs undesirable side effects. Hence, natural products continue to be more affordable and accessible than conventional drugs representing the available treatment first line for numerous worlds' population [52]. Natural products have been used lately as an alternative to prevent or overcome diabetes, as they contain a bioactive component that has a hypoglycemic potential [53]. Propolis is one of those natural products which have antioxidant capacity and marked hypoglycemic [54], hypolipidimic [25] and hepatoprotective effects [35].

Glucose hemostasis

The results of the present study showed that a single injection of 45 mg/kg bw of STZ to the rats caused a significant increase in serum glucose and blood glycosylated hemoglobin (HbA1c) levels as well as in hepatic G-6-pase activity in contrast to significant decrease in serum insulin and blood hemoglobin (Hb) levels as well as liver glycogen content as compared to the control group. These results are in accordance with the findings reported that STZ intraperitoneal administration to rats led to marked elevation of serum fasting glucose level (hyperglycemia) and hypoinsulinemia

doi: 10.41720032-745x.1000322

[23,19]. These blood glucose and insulin concentration changes had reflected β-cell function abnormality with subsequent decrease in insulin biosynthesis and secretion and impaired glucose utilization (oxidation and glycogenesis) [12]. The recent experiments done by Ghosh et al. [55] suggested DNA alkylation as the major cause for β-cell death induced by STZ resulting in significant insulin decrease and marked elevation in serum glucose level. Such suggestion was in harmony with the study of Guerrero-Berroa et al. [56] who cleared that in STZ treated rats there was total or near total loss of insulin secretion, as number of cells producing insulin were reduced. This led to decreased insulin production resulting in an enhanced gluconeogenesis and glycogenolysis leading to overall increase in blood glucose levels with gross loss of liver glycogen content as well as muscles and fats due to increased protein catabolism and lipolysis. Regarding the decrease of the hepatic glycogen content, it is in harmony with the increase of G-6-pase activity and hyperglycemia observed in the present study, in STZ-induced diabetic rats. However, hyperglycemia is accompanied by reduced insulin induced glycogen synthesis activation, which could provide an explanation for the depressed ability of liver to synthesize or accumulate glycogen in diabetes [9]. Thus, the decreased hepatic glycogen content may be associated mainly with the hyperglycemia resulted from reduced insulin production and action [12]. Alternatively, glycogen storage disruption may also associate with liver dystrophic changes leading to an inhibition of some carbohydrate metabolism key enzymes such as hexokinase, glucokinase and phosphoglucomutase and/or stimulation of others like G-6-Pase [57]. The hepatic glycogen stores depletion in diabetes, therefor, may arise from glycogenolysis increase, as indicated by the G-6-Pase activity increase which suggested being responsible for the increase of hepatic glucose output and subsequently blood glucose levels elevation [8]. In the present study, Hb content was significantly decreased, while the HbA1c level was elevated in STZ-induced diabetic rats. Such results were in accordance with the results revealed a significant increase in HbA1c level in diabetic patients and STZ-diabetic rats [57,58]. However, HbA1c % elevation and declined Hb contents, during diabetes, may be attributed to the higher levels of blood glucose and its impaired utilization as excess glucose reacts with Hb to form HbA1c and the rate of glycation is proportional to the blood glucose concentration [58]. On the other hand, in the present study, marked hypoglycemic effects were shown by propolis treatment in STZ-diabetic rats, which indicatedby the raised plasma insulin levels and hepatic glycogen contents as well as Hb levels, while significantly lowered blood glucose, hepatic G-6-pase activity and HbA1c levels to reach nearly normal control values in comparison with diabetic rats [59]. The results herein are in harmony with the findings depoted that propolis oral treatment (200 mg/kg bw) to STZ-induced type I diabetic rats daily for 5 weeks [34] and to type II diabetic rats for 8 weeks [19], ameliorated serum glucose alterations near the normal levels. This is confirmed by Al-Hariri [25] who suggested the potential use of propolis as an antidiabetic agent, attributing its hypoglycemic activity to intestinal maltase activity inhibition, thus preventing blood glucose elevation following carbohydrate intake [60,61]. Another explanation was suggested by Oršolić et al. [62] who illustrated that propolis long-term glycemic control could be due to the inhibition of hepatic glucose release, stimulation of peripheral tissues glucose uptake and/or reduced intestinal glucose absorption, which would be useful for type I DM treatment. Such suggestion is in agreement with the data obtained by Al-Hariri et al. [29] who detected that propolis treatment in STZ-induced diabetic rats is associated with high plasma insulin and/or low glucagon, that causes hepatic glucose output inhibition and peripheral tissue insulin sensitivity improvement as probable mechanisms for propolis glycemic control. Moreover, Kolankaya et al. [63] and Newairy et al. [64] propolis antioxidant components as flavonoids and many phenolic compounds may in part account for its hypoglycemic effects by enhancing the antioxidant defense system and hence protecting and/or repairing hepatic and pancreatic tissue [29]. In point of fact, the antihyperglycemic activity of propolis could be mainly attributed to its insulinogenic activity that may stimulate insulin secretion from the remnant and/or regenerated β-cells, as propolis either enhances cell activity and induces regeneration and repair of pancreatic β cells or it prevents further deterioration of β cells through its antioxidant properties [30]. This clearly confirms the possibility of propolis usage as a therapeutic adjunct for diabetes cure. Regarding the improvement in glycogen content and G-6-pase activity following propolis treatment in diabetic rats, similar results recorded by Bhadauria et al. [65] who found that 3 weeks propolis treatment (200 mg/kg bw) preserved hepatic glycogen store dramatically in diabetic rats accompanied with a significant decrease in G-6-pase activity, indicating a marked decrease in hepatic glycogenolysis, which explains the significant decrease in blood glucose levels and confirms the hypoglycemic effect of propolis extract. In harmony with these data, demonstrated that propolis extract maintained the glucose homeostasis of diabetic rats by controlling carbohydrate metabolizing enzyme activities such as G-6-pase. Interestingly, Al-Hariri [25] and Lio et al. [30] showed that diabetic rat's propolis treatment caused a marked elevation in Hb level but a marked decline in the HbA1c level compared to diabetic rats, a result that could be due to modulation in the glycemic status. Similarly, the treatment of diabetic rats with 200 mg/kg body weight propolis extract showed an obvious reduction, by 7.4%, of HbA1c level which demonstrated the anti-diabetic effect of propolis extract and suggested that propolis may reduce diabetic complications by its hypoglycemic effect[36].

Lipid profie

For lipid metabolism, STZ diabetic rats in the present work showed a great disturbance in lipid profile as they exhibited significant increase in both serum and liver total lipids (TL), total cholesterols (TC) and triglycerides (TG) in addition to serum low density lipoprotein (LDL-C) levels while a significant decrease in serum high density lipoprotein (HDL-C) level was seen compared to the control group. These results are in agreement with those obtained by Singh and Kakkar [8] and Zhou et al. [19] who recorded a significant increase in the serum and hepatic levels of lipid profile except HDL-C that decreased significantly in diabetic rats when compared to the control group, and this, unlikely, represents a coronary heart diseases risk. The abnormal high concentrations of serum lipids in diabetic rats could be mainly due to the increase in free fatty acids mobilization from the peripheral fat depots as a consequence of insulin deficiency, since insulin inhibits lipase hormone, thus, serum fatty acids excess promote its conversion into hepatic cholesterol and phospholipids, which along with formed hepatic TG excess, may be discharged into the blood in the form of lipoproteins [18]. Furthermore, the marked serum and liver hyperlipidemia characterizing the diabetic state may be regarded as a consequence of lipolytic hormones, such as catecholamines and glucagon, uninhibited actions on fat depots [59]. In type II diabetic individual, insulin-mediated lipoprotein lipase (LPL) depressed activity descends the lipoprotein clearance rate, which often reflected by elevated TG and TL levels together with excessive fat deposition in various tissues including the muscle bed [30]. On the other hand, in the present study, administration of propolis extract to diabetic rats greatly counteracted lipid profile as

doi: 10.41720032-745x.1000322

compared to diabetic group. Alves et al. [60] reported that propolis hypocholesterolemic effect results from its direct effect on liver or an indirect effect through thyroid hormones that nearly affect almost all lipid metabolism reactions pathways. These results are possibly profited by the amendment of insulin sensitivity and LPL activity suggesting that propolis might reduce insulin resistance by reducing lipogenesis and the toxic effects of lipids in liver. Zhu et al. [36] and Lio et al. [30] added that the reduction in lipid fractions by propolis may be also attributed to the decreased cholesterol absorption, degradation or elimination associated with decreased production of the major transporters of endogenously synthesized cholesterol, indicating cholesterol mobilization from extra hepatic tissues to liver where it is catabolized, in addition to its antioxidant contents such as phenolic compounds and flavonoids which may be responsible, in part for the anti-hyperlipidemic effect of propolis extract in diabetic rats. Daleprane et al. [61] suggested that propolis can lower plasma LDL-C in several ways; first, GIT cholesterol uptake inhibition; second, blood LDL-C elimination *via* LDL receptors; and finally, cholesterol-degrading enzymes (cholesterol-7-hydroxylase) increased activity. While propolis is capable of increasing ATP-binding cassette transporter A1 (ABCA1) expression, a membrane transporter that directly contributes HDL-C biogenesis by regulating cholesterol cellular efflux, since it plays a pivotal role in cholesterol homeostasis and HDL-C metabolism, which would be beneficial for atherosclerosis therapy and prevention [30].

Protein metabolism

Concerning proteins, the present study demonstrated that serum and hepatic total proteins, serum albumin and globulins levels were significantly decreased in diabetic rats. These results are comparable with those of other studies illustrating that the marked decreases in plasma total proteins, albumin and globulins levels in STZ-induced diabetic rats reflect disorders in the synthesis and metabolism of proteins as a consequence to acute liver damage [9]. However, this significant decline may be attributed also to several reasons such as increased gluconeogenesis, decreased amino acid uptake, hepatic damage and disruption and/or dissociation of polyribosomes from endoplasmic reticulum [11]. Furthermore, it seems likely to suggest that the lack of insulin would decrease amino acids incorporation into proteins and/or may decrease protein synthesis as Ene et al. [21] confirmed that insulin deficiency *in vivo* is associated with enhanced protein breakdown, amino acids levels elevation and negative nitrogen balance in diabetic rats. Herein, treatment of diabetic rats with propolis extract resulted in a significant increase in serum and hepatic total proteins, albumin and globulins as compared with the diabetic group. Similarly, intraperitoneal administration of propolis water extract at 50 mg/kg body weight to alloxan-induced diabetic mice for 7 days resulted in a significant increase in serum total proteins [62]. These results are also compatible with the findings obtained by Kolankaya et al. [63] who reported that there was a significant increase in serum albumin and globulin levels in propolis treated rat groups after administration of the extract (200 mg/kg b.w.) daily for 15 days and this may be due to marked improvement in the liver status and the hepatic functions. Also, the results are in harmony with the findings of El-Sayed et al. [34] who reported that oral treatment of STZ-induced diabetic rats with 200 mg/kg b.w of propolis, daily for 5 weeks ameliorated alterations in the plasma total proteins and animal body and tissue weights.

Liver function

Diabetes is a metabolic disease which leads to significant increase in free radicals prompting liver diseases development via fibrogenesis, inflammatory response and hepatocyte apoptosis induction [55]. The data obtained by the present study showed that serum ALT, AST and γ-GT activities as well as bilirubin level obviously increased in diabetic rats compared with normal control. These results are compatible with the findings obtained by Xie et al. [12] who found leakage of these enzymes from the liver cytosol into the blood stream indicating hepatocytes damage due to increased oxidative stress, liver dysfunction, enzymes biosynthesis disturbance with liver membrane permeability alteration. Such suggestion was in harmony with the study who observed that STZ injection for 30 days resulted in significant increase in serum transaminases activities and alkaline phosphatases in rats compared to the control group. This is confirmed by Singh and Kakkar [8] who stated that serum AST, ALT and γ-GT activities increased in STZ-diabetic rats in response to marked hepatic abnormalities. Concerning the elevated serum total bilirubin level in the present study in diabetic group, the result is in accordance with the findings obtained by El-Sharaky et al. [37] which showed that diabetes was found to increase the serum total bilirubin perhaps due to the decreased liver uptake and/or conjugation or increased bilirubin production due to accelerated RBCs hemolysis indicating presence of both hematological and liver problems. Another explanation is the excessive production of free radical in diabetes, since the clearance of serum bilirubin was associated with free radical production [2]. Lastly, plasma bilirubin level elevation may be attributed to periportal necrosis confirming liver damage incidence [37]. On the other hand, the data, herein, showed that treatment of diabetic rats with propolis water extract resulted in a significant amelioration in the liver markers serum levels and this improvement demonstrated the protective effect ofpropolisonhepatocytesstructureandfunctionindiabeticrats. These results are consistent with those of Bhadauria et al. [65] who revealed that propolis therapy attenuated the increased serum levels of these enzymes and caused a subsequent recovery towards normalization that might be due to recoupment in cell membrane stabilization and free radical scavenging action of propolis components as well as enhanced antioxidant status. Similar results were obtained by Newairy et al. [37] showed that propolis reduced plasma ALT and AST increased levels in the diabetic rats indicating that propolis tended to prevent damage and suppress enzymes leakage through cellular membranes and supporting the propolis hepatoprotective effect. These results are confirmed, also, by the findings reported by Zhu et al. [20] who posted that water propolis extract treatment (200 mg/kg bw) for 6 and 8 weeks resulted in obvious improvement of the liver lesions induced by STZ compared to diabetic rats, perhaps by transglutaminases expression down-regulating where serum AST and ALT levels were significantly decreased, suggesting propolis as a potential hepatic anti-fibrogenic and anti-cirrhotic agent, in diabetes. Additionally, bilirubin concentration, herein, was found to be markedly declined in serum of diabetic rats treated with propolis extract. This result is in agreement with the findings of Newairy et al. [37] who posted that this effect may be related to its antioxidant properties, a suggestion which is consistent with the finding that propolis is able to induce hepatoprotective effects on liver damage in mice**.** The possible mechanisms of hepatoprotective action of propolis extract may be related to its free radical scavenging activity as indicated by the MDA decrease and the improvement of the antioxidant system as revealed by GSH, SOD and CAT increased levels increase contents in the liver. Improved enzymatic biochemical parameters and histopathological observations also indicated recovered structural and functional integrity of the hepatic cells. Thus, it can be concluded that propolis extract possesses therapeutic potential against hepatic damage [65]**.**

doi: 10.41720032-745x.1000322

References

1. Verma R, Itankar PR, Arora SK (2013) Evaluation of antidiabetic antihyperlipidemic and pancreatic regeneration potential of aerial parts of Clitoria ternatea Bras Farmacogn. Rev J 23: 819-829.
2. Oche O, Sani I, Chilaka NG, Samuel NU, Samuel A, et al. (2014) Pancreatic islet regeneration and some liver biochemical parameters of leaf extracts of Vitex doniana in normal and streptozotocin-induced diabetic albino rats. Asian Pac Trop Biomed J 4: 124-130.
3. Patel DK, Prasad SK, Kumar R, Hemalatha S (2012) An overview on antidiabetic medicinal plants having insulin mimetic property. Asian Pac Trop Biomed J 1: 320-30.
4. Gireesh G, Thomas SK, Joseph B, Paulose CS (2009) Antihyperglycemic and insulin secretory activity of Costus pictus leaf extract in streptozotocin induced diabetic rats and in in vitro pancreatic islet culture. J ethnopharmacology 123: 470-474.
5. Smith-Palmer J, Brändle M, Trevisan R, Federici MO, Liabat S (2014) Assessment of the association between glycemic variability and diabetes-related complications in type 1 and type 2 diabetes. Diabetes research and clinical practice 3: 273-284.
6. Bufalo MC, Barreiro DP, Sartori DR, Sforcin JM (2009) Absence of propolis effect on plasma glycemic control and lipid metabolism in a diabetic rat model. ApiProduct and ApiMedical Sci J 1: 51-55.
7. Gailliot MT, Baumeister RF, DeWall CN, Manar JK, Plant EA, et al. (2007) Self-Control relies on glucose as a limited energy source Willpower is more than a metaphor. J Personality Social Psychol 92: 325 -336.
8. Singh J, Kakkar P (2013) Modulation of liver function antioxidant responses insulin resistance and glucose transport by Oroxylum indicum stem bark in STZ induced diabetic rats. Food and Chem Tox J 62: 722-731.
9. Manjusha, Aggarwala N, Niteshb, Guptac P (2012) Effect of petroleum ether extract of Sesbania sesban (Merr) roots in streptozotocin (STZ) induced diabetes in mice. Asian Pacific J of Tropical Biomed: 1254-1260.
10. Rajasekaran S, Sivagnanam K, Ravi KL, Subramanian S (2004) Hypoglycemic effect of aloe vera gel on streptozotocin- induced diabetes in experimental rats. J Med Food 7: 61-66.
11. Singh R, Kaur N, Kishore L, Gupta GK (2013) Management of diabetic complications A chemical constituents based approach. Ethnopharma J 150: 51-70.
12. Xie M, Chena D, Zhanga F, Willskyb GR, Cransc DC, et al. (2014) Effects of vanadium (III IV V)-chlorodipicolinate on glycolysis and antioxidant status in the liver of STZ-induced diabetic rats. Inorg Biochem J 136: 47-56.
13. Rajasekaran S, Sivagnanam K, Subramanian S (2005) Antioxidant effect of aloe vera gel extract on streptozotocin induced diabetes in rats. Pharmacol Res 57: 90-96.
14. El-Kholy WM, El-Habibi EM, El-Sawah SG (2011) The ameliorating effect of Aloe vera gel extract on the altered metabolic and antioxidant status in streptozotocin-diabetic rats Egypt. Ger Soc Zool J A Comparative physiology 133-154.
15. Yagi A, Hegazy S, Kabbash A, Abd-El wahab E (2009) Possible hypoglycemic effect of aloe vera L high molecular weight fraction on type II diabetic patients Saudi. Pharmaceut J 17: 209-215.
16. Amin AH, El-Missiry MA, Othman AI (2015) Melatonin ameliorates metabolic risk factors modulates apoptotic proteins and protects the rat heart against diabetes-induced apoptosis. Pharmacol Eur J 747: 166-173.
17. Choi BG, Vilahur G, Viles-Gonzalez JF, Badimon JJ (2006) The role of high density lipoprotein cholesterol in atherothrombosis in rats. Mt Sinai J Med 73: 690-701.
18. Jasmine R, Daisy P (2007) Hypoglycemic and hypolipidemic activity of Eugenia jambolana in streptozotocin- diabetic rats Asian J Bioch 2:269-273.
19. Zhou J, Xu G, Yan J, Li K, Bai Z, et al. (2015) Rehmannia glutinosa (Gaertn) DC polysaccharide ameliorates hyperglycemia hyperlipemia and vascular inflammation in streptozotocin-induced diabetic mice. Ethnopharmacol J 164: 229-238.
20. Takahashi Y, Zhu H, Yoshimoto T (2005) Essential roles of lipoxygenase in LDL Oxidation and development of atherosclerosis. Antioxid Redox Siginal 7: 425-431.
21. Ene A, Nwankwo E, Samdi L (2007) Alloxan-induced diabetes in rats and the effects of black caraway (Carum carvi l) oil on their body weight. Res J Medic Med sciences 2: 48-52.
22. Sirasanagandla S, Kasetti RB, Shaik AN, Natava R, Surtineni VP, et al. (2013) Antihyperglycemic and antihyperlipidemic activities of 2-(4-[(2-hydroxybenzyl) amino]-phenyl amino-methyl)-phenol in STZ induced diabetic rats. Europ Medicin Chem J 66: 400-406.
23. Arya A, Cheaha SC, Looia CY, Tahaa H, Mustafaa MR, et al. (2012) The methanolic fraction of Centratherum anthelminticum seed downregulates pro-inflammatory cytokines oxidative stress and hyperglycemia in STZ-nicotinamide-induced type 2 diabetic rats. Food and Chem Toxicol J 50: 4209-4220.
24. Mohan S, Nandhakumar L (2014) Role of various flavonoids Hypotheses on novel approach to treat diabetes. Med Hypotheses and Ideas 8: 1-6.
25. Al-Hariri MT (2012) Propolis and its direct and indirect hypoglycemic effect Family and Community Med J 18: 152-154.
26. Patel J, Ketkar S, Patil S, Fearnley J, Mahadik KR, et al. (2014) Potentiating antimicrobial efficacy of propolis through niosomal-based system for administration. Integrat Med Res J 10: 224-335.
27. Frances RH, Thyra B, Vanessa N, Anita H, Danielle V, et al. (2014) Topical application of the bee hive protectant propolis is well tolerated and improves human diabetic foot ulcer healing in a prospective feasibility study. Diabet and Complic J 28: 850-857.
28. Hongzhuan X, Zhao J, Junying M, Yajing L, Yafang C, et al. (2011) Effect of Brazilian propolis on human umbilical vein endothelial cell apoptosis. Food and Chem Toxicol J 49: 78–85.
29. Al-Hariri M, Gamal Eldin T, Abu-Hozaifa B, Elnout A (2011) Glycemic control and anti-osteopathic effect of propolis in diabetic rats. Diabet Metab Synd And Obes J 4: 377-384.
30. Lio A, Ohguchia K, Maruyamac H, Tazawac S, Arakic Y, et al. (2012) Ethanolic extracts of Brazilian red propolis increase ABCA1 expression and promote cholesterol efflux from THP-1 macrophages. Phytomedic J 9: 383-388.
31. Nirala SK, Bhadauria M, Shukla S, Agrawal OP, Mathur A, et al. (2008) Pharmacological intervention of tiferron and propolis to alleviate beryllium-induced hepatorenal toxicity. Fundam Clin Pharma 22: 403-415.
32. Fuliang HU, Hepburn HR, Xuan H, Chen M, Daya S, et al. (2005) Effects of propolis on blood glucose blood lipid and free radicals in rats with diabetes mellitus Pharma Res J 104: 147-152.
33. Yonar SM, Uralb MS, Silicic S, Yonar ME (2014) Malathion-induced changes in the haematological profile the immune response and the oxidative/ antioxidant status of Cyprinus carpio carpio Protective role of propolis Ecotoxicol and Environmental Safety J 102: 202–209.
34. El-Sayed ME, ABO-Salem OM, Aly HA, Mansour AM (2009) Potential antidiabetic and hypolipidimic effects of propolis extract in STZ-induced diabetic rats. Pak J Pharm Sci 22: 168-174.
35. Bhadauria M (2012) Combined treatment of HEDTA and propolis prevents aluminum induced toxicity in rats. Food and Chem Toxicol J 50: 2487-2495.
36. Zhu W, LI Y, Chen M, Hu F (2010) Protective effects of Chinese and Brazilian propolis treatment against hepatorenal lesion in diabetic rats. Human and Experimental Toxic J 30: 1246-1255.
37. El-Sharaky AS, Newairy AA, Badreldeen MM, Eweda SM (2007) Protective role of selenium against renal toxicity induced by cadmium in rats. Toxic J 235: 185-193.
38. Funakoshi-Tago M, Okamotoa K, Izumia R, Tagob K, Yanagisawab K, et al. (2015) Anti-inflammatory activity of flavonoids in Nepalese propolis is attributed to inhibition of the IL-33 signaling pathway. Int Immunopharmaco J 25: 189-198.
39. Koroglu P, Senturkb GE, Yucela D, Ozakpinarc OB, Urasc F, et al. (2015) The effect of exogenous oxytocin on streptozotocin (STZ)-induced diabetic adult rat testes. Peptides J 63: 47-54.
40. Trinder (1984) Acolorimetric method for determination of glucose. Ann Clin Biochem 6: 24-26.
41. Van KEG, Zijlstra WG (1961) Standardization of hemoglobinometry. Clin Chima Acta 6: 538-544.

doi: 10.41720032-745x.1000322

42. Gonen B, Rubenstein AH (1978) Estimation of glycosylated hemoglobin Diabetologia 15: 1-3.
43. Flier J, Kahn C, Jarrett D, Roth J (1976) Characterization of antibodies to the insulin receptor A cause of insulin-resistant diabetes in man. J Clin Investigation 58: 1442-1449.
44. Damsbo P, Vaag A, Hother-Nielsen O, Beck-Nielsen H (1991) Reduced glycogen synthase activity in skeletal muscle from obese patients with and without type II diabetes mellitus. Diabetologia 34: 239-245.
45. Rossetti L, Lee YT, Rutz J, Aldrige SC, Shamoon H, et al. (1993) Quantitation of glycolysis and skeletal muscle glycogen synthesis in humans Am J Physiol 265: 761-769.
46. Friedewald (1972) Determination of serum low density lipoprotein cholesterol (LDL-C) Clin Chem 25: 560-562.
47. Young DS (2001) Effects of disease on clinical laboratory tests. Clin Chem 4: 17-18.
48. Fossati P, Prencipe L (1982) Serum triglycerides determined colourimetrically with an enzyme that procedures hydrogen peroxide. Clin Chem 28: 2077-2080.
49. Zollner N, Kirsch K (1962) Microdetermination of lipids by the sulphophosphovanillin reaction. Reaction. Exp Med 135: 545-548.
50. scherwin JE, Kaplan LA, Pesce AJ, Kazmierczak SC (2003) Liver function. Clin chem 4: 492-496.
51. Chien H, Lee T, Chen C, Chiu Y, Lin Y, et al. (2015) Circulating microRNA as a diagnostic marker in populations with type II diabetes mellitus and diabetic complications. Chinese Med Association J 78: 204-211.
52. Khan V, Najmi AK, Akhtar M, Agil M, Mujeeb M, et al. (2012) A pharmacological appraisal of medicinal plants with antidiabetic potential. Pharm Bioallied J 4: 27-42.
53. Kashkooli OB, Dorcheh DD, Soofiani NM, Samie A (2011) Long-term effects of propolis on serum biochemical parameters of rainbow trout (Oncorhynchusmykiss). Ecotox and Enviro Saf J 74: 315-318.
54. Campos JF, Pereira dos Santosa U, Macorinia LFB, Felipe de Melob AMM, Balestieria JBP, et al. (2014) Antimicrobial antioxidant and cytotoxic activities of propolis from Melipona orbignyi (Hymenoptera Apidae). Food and Chem Tox J 65: 374-380.
55. Ghosh S, Bhattacharyya S, Rashid K, Sil PC (2015) Curcumin protects rat liver from streptozotocin-induced diabetic pathophysiology by counteracting reactive oxygen species and inhibiting the activation of p53 and MAPKs mediated stress response pathways. Tox Rep J 2: 365-376.
56. Guerrero-Berroa E, Schmeidlera J, Beeria MC (2014) Neuropathology of type 2 diabetes a short review on insulin-related mechanisms. Eur Neuropsychopharmacol J 24: 1961-1966.
57. Sundaram R, Naresh R, Shanthi P, Sachdanandam P (2013) Modulatory effect of green tea extract on hepatic key enzymes of glucose metabolism in streptozotocin and high fat diet induced diabetic rats. Phytomedicine J 20: 577-584.
58. Krishnan SSC, Subramanian IP, Subramanian SP (2014) Isolation characterization of syringin phenylpropanoid glycoside from Musa paradisiaca tepal extract and evaluation of its antidiabetic effect in streptozotocin-induced diabetic rats. Biomed and Prevent Nutr J 4: 105-111.
59. Subbiah R, Kasiappan R, Karuran S, Sorimuthu S (2006) Beneficial effects of aloe vera leaf gel extract on lipid profile status in rats with streptozotocin diabetes. Clin Exper Pharmacol Physiol 33: 232-237.
60. Alves MJQF, Mesquita FF, Sakaguti M, Tardivo AC (2008) Hypocholesterolemic effect of propolis' caffeic acids. Revista Brasileira de Plantas Medicinais 10: 100-105.
61. Daleprane JB, Freitasb V, Pachecoc A, Rudnickib M, Faineb LA, et al. (2012) Anti-atherogenic and anti-angiogenic activities of polyphenols from propolis. Nutr Biochemi J 26: 557-566.
62. Oršolić N, Sirovinaa D, Gajskib G, Garaj-Vrhovacb (2013) Assessment of DNA damage and lipid peroxidation in diabetic mice Effects of propolis and epigallocatechin gallate (EGCG) Mutation Res /Gen Tox and Env. Mutagenesis J 757: 36-44.
63. Kolankaya D, Selmano G, Sorkun K, Bekir S (2002) Protective effects of Turkish propolis on alcohol-induced serum lipid changes and liver injury in male rats. Food Chem J 87: 213-217.
64. Newairy AA, Salama AF, Hussien HM, Yousef MI (2009) Propolis alleviates aluminium-induced lipid peroxidation and biochemical parameters in male rats. Food and Chem Toxic J 47: 1093-1098.
65. Bhadauria M, Nirala SK, Shukla S (2007) Hepatoprotective efficacy of propolis extract. Iranian Pharmac And Therapeutics J 6: 145-154.

Author Affiliations

Top

Department of Physiology, Faculty of Medicine, Um-Alqura University, Saudi Arabia