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Propolis "bee glue" as therapeutic and protective effect on 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 supplement 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 control and propolis control, by a single dose of Alloxan(150 mg/kg).Rabbits with glycaemia were treated with alcoholic extract of propolis(50mg/kg/day) orallyfor 10 days marked significant increase ($p<0.05$) in the biochemical values,which including glucose, cholesterol, urea and creatininewere recorded in comparison with the control and diabetic groups. The protective and therapeutic groups showed significant decrease ($P<0.05$) in glucose, cholesterol, urea and creatinine in comparison with the diabetic group. While the propolishas no significant effect on the level of blood glucose, cholesterol, urea and creatinine with control group.Generally, the gradual improvement in blood values was noticed forpropolis (50mg/kg) and administration dose had a potent antihyperglycemic effect. In conclusion, the results suggest that propolis could potentially contribute for the treatment of diabetes mellitus.

Key words: Alloxan, Propolis , Blood parameter , Diabetic.

Introduction

Propolis or bee glue is a dark sticky resinous material collected by bees from exudates and bud of the plants and mixed with wax and bee enzymes. The word propolis (from the Greek pro = in defense or for, and polis = city) reflects its importance to bees, since they use it to smooth out internal walls, as well as to protect the colony from diseases and to cover carcasses of intruders who died inside the hive, avoiding their decomposition (Bankova*et al*., 2000).

Raw propolis contains impurities such as wood, wax, pollen and even dead bees, so that it is necessary a macroscopic observation of the sample in order to eliminate and to purify it before preparation of extracts. A critical step in the process of testing is the extraction of the propolis specimens that will be used in the study (Ghisalberti, 1979 ;Bankova*et al*., 1992). The color may be creamy, yellow, green, light or dark brown (Steinberg *et al*., 1996).

Propolis presents plenty of biological and pharmacological properties, such as immunomodulatory, antitumor, antiinflammatory, antioxidant, antibacterial, antiviral, antifungal, antiparasite activities, among others (Sforcin*et al*., 2000, 2001; Gekker*et al*., 2005; Orsi*et al*., 2005, 2006; Freitas*et al*., 2006 and Búfalo*et al*., 2009).

The chemical compounds of propolis are polyphenols (flavonoid aglycones, phenolic acids, and their esters, phenolic aldehydes, alcohols, and ketones), terpenoids, steroids, amino acids, and inorganic molecules (Kartal *et al*., 2003).

Polyphenols and flavonoids have biological activity that at as antibacterial, antiviral, antifungal, antioxidant and antiaging (Almeida and Menezes, 2002). Caffeic acid phenethyl ester have biological activity that at as antioxidant, anti-inflammatory, antitumor, antibacterial and antiviral (Ang*et al*., 2009).

Diabetes mellitus is a group of metabolic disorders characterized by a chronic hyperglycemia resulting from defects in insulin secretion, insulin action or both, Craig *et al*., (2009).

There are two type of diabetes: in type 1diabetes Auto-immune and non-auto-immune responses cause destruction of pancreatic β-cells (Kanatsuka*et al*., 2006). In type 2 diabetes these mechanisms break down, with the consequence that the two main pathological defects in type 2 diabetes are impaired insulin secretion through a dysfunction of the pancreatic β-cell, and impaired insulin action through insulin resistance Holt., (2004).

About 85% of all diabetics develop retinopathy, 25–50% develop kidney disease and 60–70% have mild to severe forms of nerve damage. Diabetic patients are also 2–4 times more probably to suffer a stroke American Diabetes Association., 1997). It has been reported that in long-term complications of diabetes there are changes in arteries (atherosclerosis), basement membrane of small vessels (microangiopathy), kidney (nephropathy), retina (retinopathy) and nerves (neuropathy) (Vlassara*et al*., 1984; Nishimura, 1998). Alloxan administration increased blood glucose level in diabetic control group (Szkudelski., 2001). Alloxan administration cause inhibition of hepatic glucose production persuaded by an acute escalation of blood glucose level and enhances phosphoenolpyruvatecarboxykinase gene expression, which is an imperative enzyme for the regulation of gluconeogenesis (Shao *et al*., 2005).

In the diabetic group, serum level of cholestrol was significantly increase compared to the normal control group (Hussain., 2002). High blood cholesterol is a major risk factor for heart and blood vessel disease. When cholesterol levels are too high, some cholesterol gets deposited on the walls of the blood vessels. Over time, these deposits can build up and become hard lumps called plaque. This can cause the blood vessels to narrow, harden and decrease blood flow, possibly leading to other serious health risks including hypertension, problems with blood clotting, heart attack or stroke. (American Diabetes Association, 2006). Renal dysfunction as a result of diabetes mellitus can be assessed by serum creatinine and urea. Increase in creatinine and urea occurs when there is renal dysfunction or damage (Aldler*et al*., 2003).

Materials and Methods

1. Laboratory animals

Adult male rabbits were purchased from local market of AlmaddinahAlmonawrah USK. They weighed between 350g to 450g. They were fed on natural plant diet and provide with diet and water *ad libitum* (Khushk *et al*., 2010)

1.1. Experimental design

Animals of this study were divided into five groups (each of 5) were randomly divided; the negative control group, positive (diabetic) control group, propolis control group and two diabetic treatment groups.All rabbits except normal control and propolis control were injected with one dose of alloxan monohydrate, concentration 150 mg/kg body weight.Diabetic control group did not treat with propolis. The treated animals were subdivided into two groups protective and therapeutic groups. One oral concentrations of propolis extract were investigated (50mg/kg/day). 1ml of propolis dose administered orally by syringe daily for 10 days.

a. Propolis sample

Traps are basically screens or special plates with small holes which simulate cracks in the hive walls . Bees try to seal the holes and thus fill the trap with propolis. The most economic trap design is an inner cover with a large hole, covered with regular nylon screen, secured in place by the points of nails and a perforated frame . However, to avoid contamination with wax, the screen should not touch the top of the frames. The total area exposed by a screen may have to be varied according to the bees and local conditions. Trap harvested propolis usually fetches a better price because of its cleaner and therefore of better quality. Light, and in particular air circulation are important to stimulate propolis use. Accordingly, traps placed on top of hives should be covered but the hive cover needs to be propped opened slightly to increase air circulation and to allow in some light .so, propolis samples were collected by described methods before, were gathering from different potinecal region (Australia and Saudi Arabia).

b. Preparation of ethanolic extract propolis

Propolis samples were extracted by maceration at room temperature, with occasional shaking, in the proportion of 10 g of Australian propolis to 100 ml of solvent (ethanol 80%v/v), extracts were obtained after 7 days of maceration and the ethanolic extracts werethen filtered by Whatman (No.1) filter paper and incubated at room temperature until ethanol evaporated and the product obtained a honey-like consistence are referred to as ethanolic extract propolis, this method was reported by (Ildenize*et al*, 2004).

c. Induction of diabetes:

Induction diabetic mellitus: the animals were fasted for 18 h then allowed access to water before induction of diabetes. Alloxan monohydrate administered intraperitoneally after dissolve in sterile normal saline(0.9%) at single dose of 150mg/kg of body weight after estimation of blood glucose level those animals that have over 170 mg/dl serum glucose they were considered diabetic and used for the further experiment, Since alloxan is capable of producing fatal hypoglycemia, animals were treated with 20% glucose solution intraperitoneally after 6 h (Szkudelski, 2001).

d. Collection of blood by cardiac puncture

Rabbit were dissected in order to withdraw blood from the heart and appropriate needle is used for blood sample collection with or without thoracotomy. Blood sample will be taken from the heart, preferably from the ventricle slowly to avoid collapsing of heart (Paulose and Dakshinamurti, 1987andYoburn*et al*., 1984).

e. Centrifugation and storage of blood sample

Serum sample were obtained by centrifugation of sample at 4000 rpm for 20 minutes, and were stored at -20 °C until being used for analysis. Stored serum samples were analyzed for glucose, cholesterol, urea, creatinine. Were assayed by commercial kits according to the procedure outlined by the manufacturer .

f. Chemical Analysis:

Blood Glucose and cholesterol tests (spinereact kits, Spain)were used according to (Kaplan, 1984 and Naito, 1984) respectively.in addation the urea and Creatinine tests (diamond and BioMed kits ,USA)wereused according to. (Young, 2001 and Jaff'e, 1886) ,respectively.

g. Statistical analysis

Analysis of data was performed by Minitab 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.

Results and Discussion

1. Effect of propolis extract on serum glucose of diabetic rabbits

Data in Table (1 and fig.1) shows and compares changes in the blood glucose levels in different groups. There was no significant change in the level of blood glucose between the control groups (86.850 ± 0.478) mg/dl and propolis control groups (89.402 ± 0.678) mg/dl through the experimental period. Results are agreement with (Michelle *et al*., 2009) that propolis did not influence glucose concentrations .Alloxan administration increased blood glucose level in diabetic group which recorded (172.47 ± 0.873) mg/dl when compared with control groups .

The results showed that alloxan at concentration of 150 mg/ kg successfully causes diabetes in rabbits. This agree with (Albushabaa, 2014 and Hadi, 2014). The increase in blood glucose level is due to that the alloxan acts as a cytotoxin for beta-cells of the islet of Langerhans, causes diabetes by inducing cell necrosis. (Jorns*et al*., 1997 and Ledoux*et al*., 1986). The reactive oxygen species mediates the cytotoxic action with the increase in cytosolic calcium concentration, leading to rapid beta-cells destruction (Szkudelski, 2001) this results into decreased insulin secretion and elevated blood glucose level (Deewanjee, 2008). The alloxan induces diabetes by partial destruction of the β-cells of islets of Langerhans (Szkudelski, 2001).

TABLE 1. Effect of propolis extract on tested blood parameter of different groups

Group	Glucose (mg/dl)	Cholesterol (mg/dl)	Urea (mg/dl)	Creatinine (mg/dl)
Control	86.850 ± 0.478^{c}	62.63+-2.72^{c}	24.439±0.531^{b,c}	1.1802 ± 0.0750^{c}
Control propolis	89.402 ± 0.678^{c}	59.95+-1.25^{c}	23.278±0.761^{b,c}	1.1960 ± 0.0370^{c}
Control Diabetic	172.47 ± 0.873^{a}	106.74+-2.39^{a}	29.37±1.16^{a}	1.7160 ± 0.0496^{a}
Protective	108.44± 3.22^{b}	73.49+-2.26^{b}	21.410±0.890^{c}	1.3762 ± 0.0286^{bc}
Therapeutic	99.58 ± 6.52^{c}	77.91+-1.30^{b}	26.566±0.477^{a,b}	1.4258 ± 0.0569^{b}
p-value	0.01	0.01	0.01	0.01

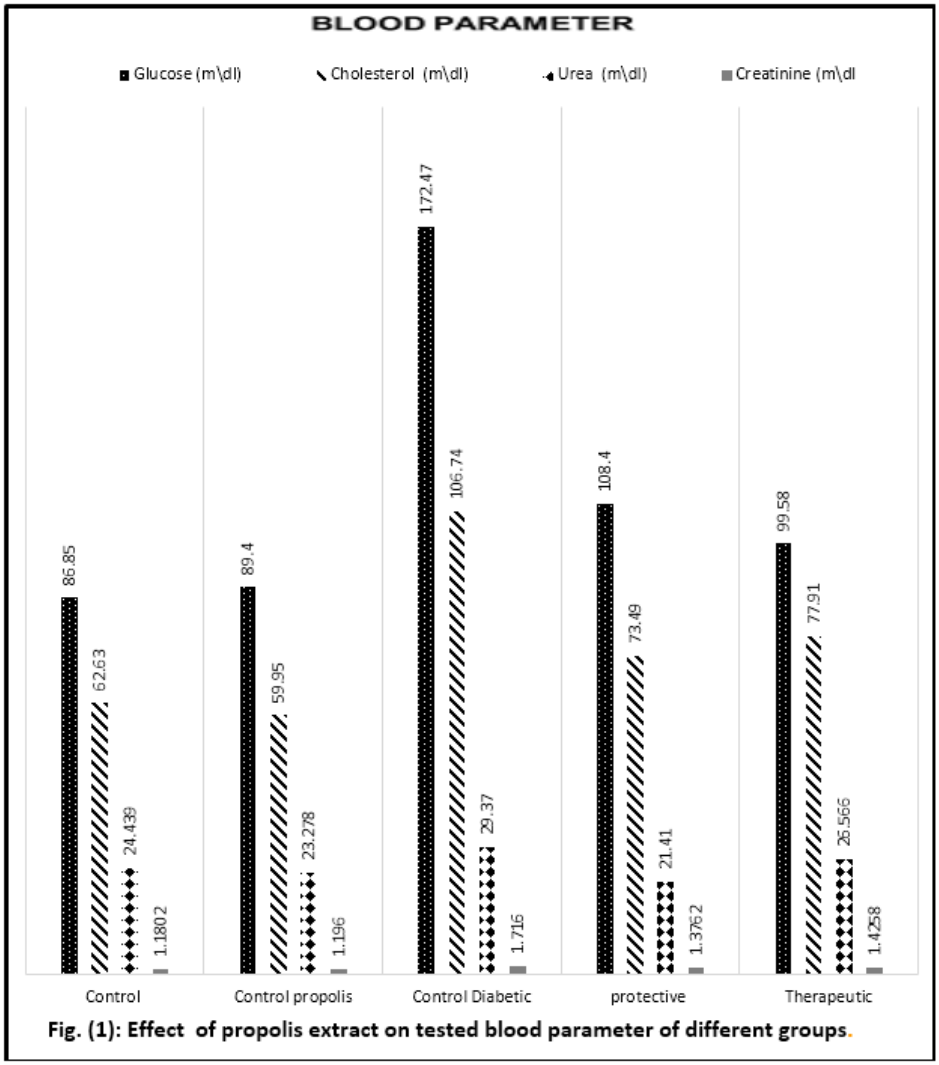

Fig. (1): Effect of propolis extract on tested blood parameter of different groups.

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) . Increase in blood glucose also 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).

Protective and therapeutic groups showed significant (P<0.05) reduced in blood glucose level(108.44± 3.22) (99.58 ± 6.52) mg/dl respectively comparing with diabetic group. This result in line with data reported by (Matsui *et al*.,2004) it was found that thepropolis compounds containing tri-CQA. These compounds are thought to play a role in controlling blood glucose diabetic by decreasing glucose absorption through the inhibition of intestinal maltase activity, this effect was more beneficial in modulating postprandial blood glucose level rise upon dietary carbohydrate intake. Other compounds such as luteolin are thought to play a role in the antidiabetic effect. This result conforms to the findings of (Wang and Li, 2004 and Murata *et al*., 2004) the significant hypoglycemic activity of propolis may suggest that, propolis exacts this activity by direct and indirect mechanism (Wang and Li, 2004). Propolis has acted indirectly by stimulating the few surviving β- cells to secrete more insulin rather than aiding the regeneration of necrotic β-cells of the pancreas (Murata *et al*., 2004). Also, it has been reported that the water extract of propolis prevented β-cells destruction by inhibiting IL- β generation and NO synthase activity (Matsushige*et al*., 1996).

2. Effect of propolis extract on serum cholesterol of diabetic rabbits

From Table (1 and fig.1) shows the serum levels of cholesterol in all groups. There was no significant change in the level of cholesterol between the propolis groups which record (59.95±1.25) mg/dl and the control groups (62.63±2.72) mg/dl. This result was agreement with (Biavatti, 2003; Kang *et al*., 2007 and Kedzia *et al*., 1988).

The serum level of cholesterol was significantly (P<0.05) increased in the diabetic group (106.74±2.39) mg/dl compared to the control group. This result was agreement with (Fuliang, 2005). The abnormal high concentration of serum lipids in the diabetic subject is mainly due to increase in the mobilization of free fatty acids from the peripheral fat depots (Hussain, 2002). Also, the rise in cholesterol level which is associated with insulin deficiency, is attributed to increase in plasma concentration of VLDL and LDL which may be due to increased hepatic production of VLDL or decreased removal of VLDL and LDL from the circulation (Ganong, 2005 and Sukkar*et al*., 1993). This result was agreement with (Tasawar*et al*., 2011 and Nordestgaardand Zilversmit1988).

The serum level of cholesterol was significantly (P<0.05) decrease in protective and therapeutic groups (73.49±2.26) (77.91±1.30) mg/dl respectively comparing with diabetic group (106.74±2.39) mg/dl. Propolis treatment may indicate improvement of liver function in rabbit and that may be due to the highest biological activity and nutritive values contents in bee propolis, which are responsible for the prevention of lipid peroxidation(kamel*et al*., 2007). (Matsui*et al.*, 2004) reported that decrease of cholesterol levels in rabbits may be directly related to the influence of bee propolis on lipid metabolism. This result was agreement with (Fuliang*et al.*, 2005; Gumieniczek, 2002 and Eraslan*et al.*, 2007).

3. Effect of propolis extract on serum urea and creatinineof diabetic rabbits

Table (1 and fig.1) shows the serum levels of urea and creatinine in all groups. There was no significant change in the level of urea and creatinine between the propolis groups which record (23.278±0.761) (1.1960 ± 0.0370) mg/dl respectively and the control groups (24.439±0.531) (1.1802 ± 0.0750) mg/dl respectively. This result was agreement with the finding of (Biavatti, 2003; Akgul*et al*., 1997 and Kamel*et al*., 2007). The evidence that propolis does not induce kidney damage came from urea and creatininedeterminations (Nagyova *et al.*, 1994).

The serum level of urea and creatinine were significantly (P<0.05) increased in the diabetic groups (29.37±1.16) (1.7160 ± 0.0496) mg/dl respectively compared to the control group. The significant increase might be due to increased synthesis from the damaged pancreatic cells caused by alloxan injection (Adesokan*et al*., 2009). Serum creatinine and urea are established markers of Glomerular Filtration Rate (GFR). Though serum creatinine is a more sensitive index of kidney function compared to serum urea level. This is because creatinine fulfills most of the requirements for a perfect filtration marker (Perrone*et al*., 1992). Raised serum creatinine and urea levels in diabetic groups may indicate a pre-renal problem such as volume depletion. The high creatinine levels observed in diabetic may be due to impaired function of the nephrons (Judykay, 2007). The increase in urea nitrogen in diabetes may be accounted for by enhanced catabolism of both liver and plasma proteins that accompany gluconeogenesis (Prakasam*et al*., 2004).

Significant decrease was showed in protective (21.410±0.890), (1.3762 ± 0.0286) mg/dl respectively and therapeutic (26.566±0.477) (1.4258 ± 0.0569) mg/dl respectively when compared with diabetic groups. This is due to the propolis extract significantly ameliorated the clearance of this metabolite by the kidney, thus restoring the serum level of urea and creatinine to normal. This is in agreement with the findings of (Yamabe*et al*., 2006). This effect is probably due to the antioxidant protective effect of propolis which could have accumulated in the cells of

the proximal convoluted tubule of the kidney where propolis was reported to be collected and secreted (Sun *et al.*,2000). Caffeic acid phenethyl ester (CAPE), a biological active component of propolis was found to improve renal function tests in a rat model with lithium-induced renal tubular damage and oxidative stress (Oktem*et al.*,2005). Therefore propolis protected the status of cellular biomolecules towards normal by improving the cellular metabolism and reversed the hepatic necrosis and renal tubular damage(Bhadauria and Nirala, 2009).

Conclusion

In conclusions this study revealed that ethanolic extract of propolis at 50 mg/kg possesses antihyperglycemic property as well as improves blood glucose , cholesterol, urea and creatinine in alloxan-induced diabetic rabbits. Ethanolic extract of propolis would be safer and useful in treating diabetes mellitus in rabbits.

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التأثير العلاجي والوقائي للبروبوليس على أرانب مصابة بمرض السكري

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لقد أجريت هذه الدراسة بهدف تقييم تأثير المعاملة بالبروبوليس على أرانب التجارب المصابة بمرض السكري. فقد تم معاملة أرانب التجارب بمادة أللوكسان والتى تسبب مرض السكري عند حيوانات التجارب وتم تقسيم حيوانات التجارب إلى مجموعتين؛ مجموعة عوملت بالبروبوليس قبل المعاملة بمادة أللوكسانلدراسة التأثير الوقائي للبروبوليس ومجموعة عوملت بأللوكسانقبل المعاملة بالبروبوليس لدراسة التأثير العلاجي للبروبوليس وتم إعطاء حيوانات التجارب البروبوليس بمعدل 150 ملليجرام/ كيلو جرام من الأرانب عن طريق الفم وذلك لمدة عشرة أيام متتابعة وبعد إنتهاء التجربة تم تشريح حيوانات التجارب وتجميع الدم منها وفصل سيرم الدم لقياس الجلوكوز والكوليستيرول واليوريا والكرياتينين فى سيرم الدم.

وقد أظهرت النتائج تأثيرا معنويا للمعاملة بالبروبوليس وقائيا وعلاجيا من خلال قياس الجلوكوز والكوليستيرول واليوريا والكرياتينين بالمقارنة بالمجموعة المصابة بمرض السكري ولم يتم معاملتها بالبروبوليس وكان الفرق غير معنوي فى كل القياسات عند المقارنة بالمجموعة غير المصابة بمرض السكري وغير المعاملة بالبروبوليس.

وبذلك توضح الدراسة أن البروبوليس يمكن أن يكون له تأثيرا علاجيا ووقائيا ضد مرض السكري.