Effect of propolis and *Feoniculumvolger* on hematological parameters and kidney functions in alloxan diabetic rats

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Abstract: Background: propolis is high efficient antioxidant antimicrobial, anticancer and antidiabetic agent. Propolis is collected by bees from trees. Foeniculum vulgare is antioxidant and antidiabetic agent this is due to it includes transanithol substance and other active ingredients. The aim of work is: To see the effect of these natural products on blood cells and hematology in diabetic rats and on kidney functions in addition to see its effects on kidney tissue. **Materials and methods:** Eighty rats were divided to eight groups according to the dose of both propolis and *Foeniculumvolgare* the hematological parameters, kidney function tests were analyzed in addition to sections in the kidney using Hematoxylin and Eosin stain were examined notice all groups are diabetic through induction with alloxan except the negative control. **Results:** data shows significant increase in RBCs, Hb concentration, Hct % and monocytes where lymphocytes and neutrophil shows significant decrease in addition to both ameliorates destructive effects of diabetes on kidney tissues especially on glomeruli and Bowman's capsule. **Conclusion:** propolis and *Foeniculum vulgar* has anti anemic and improve kidney.
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1. Introduction

Diabetes mellitus (DM) is a disease caused by inherited or acquired deficiency in production of insulin by B cells of pancreas or can happen by the ineffectiveness of the insulin so it considered as chronic disease it is cause metabolic disorder affecting carbohydrate, fat and protein metabolism affecting carbohydrate, protein and fat metabolism characterized by hyperglycemia glucose, urea and negative nitrogen balance. It occurs mainly due to insulin secretion lack or insulin action resistance or both (Boddupalli et al., 2012).

It is the most dispersed disease in the world affecting 25% of population and afflicts 150 million people and set to rise to 300 million by 2025. Regions with great vulnerability are Asia and Africa (Osadebe et al. 2014).

Alloxan is one of the potent methods employed in inducing diabetes in experimental animals. It selectively destroy the insulin-producing beta cells of the pancreas by oxidation of essential sulfhydryl (-SH group), inhibition of glucokinase enzyme, generation of free radicals in addition to disturbances in intracellular calcium homeostasis (Szkudlski, 2001 and Dhanesha et al., 2012).

Hyperglycemia increases in the increase level of reactive oxygen species causes autoxidative glycosylation of cell membranes, destruction of the antioxidant systems, lipid peroxidation and tissue injury (Amin et al., 2013 and Baynes, 1991).

Alloxan is unstable and hydrophilic substance. Its half-life at neutral PH and 37 C is about 1.5 min and is longer at lower temperature (Lenzen, 2008). Hyperglycemia is responsible for the intense oxidative stress in diabetes and the toxicity and it is one of the important sources of reactive oxygen species (Giugliano et al., 1996).

Diabetes resulted from lipid peroxidation which plays an important role in production of free radicals and oxidative stress (Halliwell and Gutteridge, 1994). Antioxidant defense system counter act the destructive effects of free radicals by attenuating or omitting their activities (Afshari et al., 2007).

In diabetes mellitus the oxidative stress exceeds the body's antioxidant defense mechanisms. In addition, oxidative stress and free radicals have been reported to play a significant role in diabetic complications (Hamada et al., 2009) and treatment with antioxidants is responsible for reduction of these complications (Yilmaz et al., 2004). Propolis is produced by honey bee it has biological properties it has been intensively used in health foods (Hassan, 2014).

Propolis has hypolipidemic, antioxidant and hypoglycemic activity (El-Sayed et al., 2009) which can be used to prevent or delay the appearance of diabetic complications. Its hypoglycemic activity has been attributed to inhibition of intestinal maltase activity, preventing rise of blood glucose following carbohydrate intake. Propolis enhances the antioxidant

defense system (Matsui et al., 2004) and protects pancreatic tissue (El-Sayed et al., 2009). Propolis possess several biological activities, among which its oxygen radical scavenging activity (Chen et al., 2004).

Propolis is the most important chemical weapon of bees against pathogenic microorganisms, propolis has been used as a remedy by humans since ancient times. Propolis is a resinous, sticky substance collected by honey bees from the sap, leaves and buds of plants and then mixed with secreted bees wax (Ahuja and Ahuja, 2011). The main chemical classes present in propolis are flavonoids, phenolics and other various aromatic compounds. It has been used in folk medicine due to its several pharmacological properties (Abdul-Hadi, 2014).

Effect of diabetes on kidney:

Kidneys are affected physiologically and morphologically in diabetes. The ability of the kidney to keep the level of metabolites such as, creatinine, urea and uric acid in addition to ions at optimum level and in another direction maintain stable internal environment confers on it a great homeostatic function however, the level of these metabolites increases greatly due to renal impairment resulting from diabetes mellitus (Shokeen et al., 2008).

Foeniculum vulgare:

Medicinal plants are considered to be less toxic and free from side effects then synthetic drugs (Santhakumari et al., 2003). Prolonged treatment with petroleum ether fraction of the *Foeniculum vulgare* extract confirmed the improvement in blood glucose, lipid profile and other parameters in diabetic rats (Dongare et al., 2012). Many phytoconstituents responsible for anti- diabetic effects is isolated from hypoglycemic plants (Singh et al., 2012). One of such plants is *Foeniculum vulgare* (FV). *Foeniculum vulgare* is a member of family Apiaceae this plant is an aromatic plant (Kazemi et al., 2012 and Ozbek et al., 2013). *Foeniculum vulgar* has wound healing effect and includes antibacterial peptides (Al Akeel et al., 2017).

By analysis of fennel the consists is 6.3% moisture, protein 9.5%, Fat 10%, minerals 13.4% fiber 18.5% and carbohydrates 42.3%. The mineral and vitamin contents are calcium, iron, phosphorus, sodium, potassium, thiamine, niacin, riboflavin and vitamin. Main components of *Foeniculum vulgare* are transanisol (50-70%), estrogen-dianthol. Flavonoids and organic acids (Kazemi et al., 2012 and Kaur and Arora, 2010). Anethole has a chemical structure similar to a chemical substance called dopamine, naturally present in the body. Dopamine is known to have a relaxant effect on the intestine and perhaps, explains why fennel has a beneficial effect on infantile colic. Also F.v. have antimicrobial properties. So, it is used in traditional medicine as antiviral and antibacterial (El-Soud et al., 2011).

Mhaidat et al., (2015) concluded that *Foeniculum vulgare* has antihyperglycemic activity in diabetic rats. *Foeniculum vulgare* showed antihyperglycemic activity in diabetic rats it also showed potential to restore some of the cardiovascular, renal and hepatic complications of diabetes. Thus the foeniculum vulgare extract might be potential future herbal remedy for diabetes and its complications. Mhaidat et al., (2015) reported that administration of *Foeniculum vulgare* extract has effective role in preventing polydipsia and elevated levels of blood glucose so, it shows antidiabetes, and activity in addition to diabetes associated increase in urea and createnine were restored at least partially.

Foeniculum vulgare is recommended for diabetes and kidney stones. A previous study showed that F. vulgare essential oil corrected hyperglycemia (El-Soud et al., 2011). Mostafa et al., (2015) reported that foeniculum vulgare Mill contains transanethole which is the major constituent and also has antioxidant and antidiabetic activity. Faudale et al., 2008 and Ozbek et al., 2003 stated that foeniculum vulgare has antifungal, antibacterial, antioxidant, antidiabetic and hepatoprotective activities.

Barros et al., 2009 and Carlsen et al., 2010 stated that fennel is highly recommended for diabetes where reactive oxygen species are involved in the oxidative stress that propably one of the causative factors of the disease. Fennel contain trans anethole which possess hypoglycemic activity because it can significantly reverse the altered activities of key enzymes involved in the metabolism of carbohydrates to near normal (El- Sheikh et al., 2015). Fennel was found to control the fasting glucose, lipid parameters and glycated haemoglobin in diabetic rats (Dongare et al., 2012).

2. Materials and methods

All animals studies were conducted in accordance with criteria of the investigations and Ethics committee of the community laws governing the use of experimental animals.

Experimental Animals:

The male albino rats (n=80) at average weight of (190±10) at the beginning of the experiment. Obtained from the Egyptian holding company for biological product and Vaccines were used as experimental animals. The rats were transferred to the experimental environment one week prior to the initial of the experiments as to ensure their environmental adaptation. The rats were transferred to the animal house in Zoology Department, Faculty of Science, Al-Azhar University; the rats were housed in regular designed cage and maintained in condition of good

ventilation, normal temperature, and humidity range. Five rats were placed into each cage. Feed and water were provided *adlibitum* to the animals.

Induction of diabetes

The animals were fasted overnight. Diabetes was induced by single intraperitoneal (i.p) injection of Alloxan monohydrate (148mg/kg) in sterile normal saline (0.9%). The diabetics rats was determined 72hours after Alloxan administration through the tail, using the one touch ultra-glucometer (Glucodoctor). Weekly record of blood glucose level was taken afterwards.

Propolis:

Propolis was obtained from hives of royal bee company Cairo, Egypt. During spring and summer seasons of 2014.

Form of the agent:

Bulk of glue like brown ishmaterial resulted from scrapping off the frames of beehives.

Preparation:

Propolis bulks were cut into small pieces and mixed with deionized water and shacked at 95^{O}c for2hoursaccordingto therapeutic dose. Then cooled to room temperature and centrifuged at 1500 r.p.m for 5 minutes to obtain the supernatant **(El-Akabawy *et al.*, 2004). This occurs in** genetic engineering center Al-Azhar University

Foeniculum vulgare:

Foeniculum vulgare seeds were collected from the local market in Egypt and identified by its morphological and microscopically characters.

Preparation

Foeniculum vulgare extracted by distilled water using soxhlet apparatus according to the Association of Official Analytical Chemists **(AOAC, 1970)** in physiologylab. faculty of science Al Azhar University.

Experimental design:

The patch of animals was distributed into eight groups as the following:

Group1 control (C): negative control of normal rats, (n=10Rats) rats of this group were neither treated nor injected by alloxan.

Group 2Diabetes Mellitus (DM): positive control of Alloxan injected rats, (n=10 Rats) rats of this group were injected by Alloxan 148mg/kg intraperitoneal.

Group 3 Diabetes Mellitus+200 propolis (DM+200Pro): Rats of this group were injected with Alloxan 148 mg/kg intraperitoneal and treated with 200mg/kg of propolis.

Group 4 Diabetes Mellitus + 400 propolis (DM+400Pro): Rats of this group were injected with alloxan 148mg/kg intraperitoneal and treated with 400mg/kg of propolis. **Group5Diabetes Mellitus + 200*Foeniculum vulgare* (DM+200FV)**: Rats of this group were injected with Alloxan 148mg/kg intraperitoneal and treated with 200mg/kg of *Foeniculum vulgare*.

Group 6 Diabetes Mellitus+400 *Foeniculum vulgare* (DM+400FV): Rats of this group were injected with Alloxan 148 mg/kg intraperitoneal and treated with 400mg/ kg of *Foeniculum vulgare*.

Group 7 Diabetes Mellitus +200 propolis+200 *Foeniculum vulgare* (DM+200Pro+200FV): Rats of this group were injected with Alloxan148mg/kg intraperitoneal and treated with (200 mg/ kg of *Foeniculum vulgare*+ 200mg/kgof propolis).

Group 8 Diabetes Mellitus+400propolis+400 *Foeniculum vulgare* (DM+400Pro+400FV): Rats of this group were injected with Alloxan148mg/kg intraperitoneal and treated with (400 mg/kg of *Foeniculum vulgare*+ 400mg/kg of propolis).

The duration of treatment for one month.

Hematological study:

Blood samples were collected from animals from retro- orbital venousplexus; part of the blood was collected in EDTA (Ethylene Diamine Tetra Acetic Acid) for hematological study.

The erythrocytes number (RBCs), Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration (MCHC), The leukocyte count (WBCs), differential leukocyte count, platelets count, Hematocrit (Hct) % and Hemoglobin (Hb) concentration were estimated by blood cell counter (sinothinker) according to **(Zaahkouk, 2006)**

The other part of the blood was collected in non-Heparinized tubes then centrifuged at 3,000 R.P.M for 10 minutes then the collected serum was frozen for biochemical analysis.

At the end of experimental period, animals were fasted overnight and following diethylether anesthesia. Blood samples were collected from all animals through retro-orbital venous plexus. Put into chilled non heparinized tubes, serum was obtained by centrifugation at 3000r.p.m for 10minutes; sera were frozen at -20^{O}c for kidney functions.

Determination of kidney function tests:

1- Determination of serum blood urea nitrogen (mg/dl) concentration:

Serum BUN was determined according to the method of **First *et al.* (2003);** using kit from Elitech diagnostic Co. France.

2- Estimation of serum creatinine concentration (mg/dl):

Serum creatinine level was determined according to the method described by (**Newman and Price, 2001)** using kit from Elitech diagnostic Co. France.

Principle

The rate of formation of a coloured complex between creatinine and alkaline picrate is measured. The effects of interfering substances are reduced using

the kinetic procedure at wavelength 500nm, and read against distilled water.

3- Determination of serumuric acid level (mg/dl):

Serum creatinine level was determined according to the method described by **Barham and Trinder (1972)** using commercial kit purchased from Bio-diagnostic Company Egypt.

3. Results

A. Hematological studies

1- R. B. Cs shows a significant increase ($p<0.05$) in Control (Nondiabetic), Diabetic+treated with Propolis 200mg, Diabetic+treated with *F. vulgar* 400mg, Diabetic+treated with *F. vulgare* 200mg, Diabetic + treated with (*F. vulgare* 400mg+Proplis 400mg) when compared with Diabetic group (positive control) as presented in table (1) Where Mean and S. E was (**4.58±0.25**) in Positive control (Diabetic) and were (**5.86±0.12**), (**5.33±0.2**), (**5.45±0.07**), (**5.47±0.29**), (**5.28±0.06**) respectively.

2- W. B. Cs shows a significant decrease ($p<0.05$) in Control (Nondiabetic), Diabetic+treated with Propolis 200mg, Diabetic+treated with *F. vulgare* 400mg, Diabetic+treated with *F. vulgare* 200mg, Diabetic + treated with (*F. vulgare* 200mg+Proplis 200mg), when compared with Diabetic group (positive control) as shown in table (1) Where Mean and S. E was (**13.9±0.72**) in Positive control (Diabetic) and were (**8.88±0.88**), (**6.2±1.25**), (**9.07±0.63**), (**8.36±1.29**), (**8.1±0.66**) respectively.

Table (1): The means ± standard error (SE) of RBCs, WBCs and PLTs counts in induced-diabetic rats with alloxan and treated with Propolis and *F. vulgare* doses for one month.

Groups \ Parameters		RBCs	WBCs	PLTs
Control (Non-Diabetic)	**Means ± SE**	**5.86a ±0.12**	**8.88a ±0.88**	**203.8 ±42.83**
(positive control) (Diabetic)	**Means ± SE**	**4.58b ±0.25**	**13.9c ±0.72**	**208.67 ±51.03**
Diabetic + treated with Propolis 200mg	**Means ± SE**	**5.33ac ±0.2**	**6.2b ±1.25**	**187.25 ±31.26**
Diabetic + treated with Propolis 400mg	**Means ± SE**	**5.26abc ±0.3**	**13.66c ±0.71**	**161.33 ±28.04**
Diabetic + treated with *F. vulgare* 400mg	**Means ± SE**	**5.45ac ±0.07**	**9.07a ±0.63**	**162.75 ±25.46**
Diabetic + treated with *F. vulgare* 200mg	**Means ± SE**	**5.47ac ±0.29**	**8.36ab ±1.29**	**175 ±33.64**
Diabetic + treated with (*F. vulgare* 400mg + Propolis 400mg)	**Means ± SE**	**5.28ac ±0.06**	**14.233c ±1.37**	**201 ±5.29**
Diabetic + treated with (*F. vulgare* 200mg + Propolis 200mg)	**Means ± SE**	**5.22bc ±0.4**	**8.1ab ±0.66**	**202.67 ±53.05**
Fratio		**2.79**	**9.29**	**0.941**
Probability		*	***	**N.S**

Mean with dissimilar superscript letter are significantly different at ($P<0.05$) N.S =non-significant ($p<0.05$)=*, ($p<0.001$) =***

3- **Haemoglobin (Hb)** shows a significant increase ($p<0.05$) in Control Non Diabetic, Diabetic+ treated with Propolis 200mg, Diabetic+treated with Propolis 400mg, Diabetic+treated with *F. vulgare* 400mg, Diabetic+treated with *F. vulgare* 200mg, Diabetic+treated with (*F. vulgare* 400mg+Proplis 400mg), Diabetic + treated with (*F. vulgare 200mg*+Propolis 200mg) when compared with Diabetic group (positive control) as shown in table (2) Where Mean and S. E was **(11.73±0.37)** in Diabetic group (positive control) and were **(13.58±0.29), (14.82±0.31), (13.9±0.79), (14.7±0.17), (14.93±0.86), (13.6±0.41), (13.86±1.27)** respectively.

4-**Hematocrit (Hct)** shows a significant increase ($p<0.05$) in Control (Non Diabetic), Diabetic+ treated with Propolis 200mg, Diabetic+treated with Propolis 400mg, Diabetic+treated with *F. vulgare* 400mg, Diabetic+treated with *F. vulgare* 200mg, Diabetic+treated with (*F. vulgare* 400mg+Proplis 400mg), Diabetic + treated with (*F. vulgare* 200mg+ Propolis 200mg) when compared with Diabetic group (positive control) as shown in table (2) Where Mean and S. E was **(28.16±1.59)** in Diabetic group (positive control) and were **(35.78±0.77), (35.65±0.63), (34.83±1.12), (36.4±0.45), (36.73±1.76), (34±1.06), (32.63±1.96)** respectively.

Table (2): The means± standard error (SE) of Hemoglobin concentration and hematocrit percentage in induced-diabetic rats with Alloxan and treated with Propolis and *F. vulgare* doses for one month.

Parameters / Groups		Hb	Hct
Control (Non-Diabetic)	**Means ± SE**	**13.58a ±0.29**	**35.78a ±0.77**
(positive control) (Diabetic)	**Means ± SE**	**11.73b ±0.37**	**28.16b ±1.59**
Diabetic + treated with Propolis 200mg	**Means ± SE**	**14.82a ±0.31**	**35.65a ±0.63**
Diabetic + treated with Propolis 400mg	**Means ±SE**	**13.9a ±0.79**	**34.83a ±1.12**
Diabetic + treated with *F. vulgare* 400mg	**Means ± SE**	**14.7a ±0.17**	**36.4a ±0.45**
Diabetic + treated with *F. vulgare* 200mg	**Means ± SE**	**14.9a ±0.86**	**36.73a ±1.76**
Diabetic + treated with (*F. vulgare* 400mg+ Propolis 400mg)	**Means ± SE**	**13.6a ±0.41**	**34a ±1.069**
Diabetic+treated with (*F. vulgare* 200mg+ Propolis 200mg)	**Means ± SE**	**13.86a ±1.27**	**32.63a ±1.96**
Fratio		**2.97**	**5.50**
Probability		*	***

Mean with dissimilar superscriptletterare significantly different at (P<0.05) (p<0.05) =*, (p<0.001)=***

Table (3): The means± standard error (SE) of Erythrocyte indices (MCV, MCH and MCHC in rats subjected to Alloxan and treated with Propolis and *F. vulgare* doses for one month.

Parameters / Groups		MCV	MCH	MCHC
Control (Non-diabetic)	**Means ± SE**	**64.7 ±1.59**	**24.54 ±0.97**	**38.66 ±0.72**
Positive control (Diabetic)	**Means ± SE**	**61.53 ±3.5**	**24.9 ±1.13**	**40.16 ±0.72**
Diabetic +treated with Propolis 200mg	**Means ±SE**	**67.2 ±1.76**	**27.65 ±0.12**	**39.8 ±1.01**
Diabetic +treated with Propolis 400mg	**Means ± SE**	**66.46 ±0.15**	**26.36 ±0.39**	**40.35 ±0.68**
Diabetic +treated with *F. vulgare* 400mg	**Means ± SE**	**66.9 ±0.78**	**26.95 ±0.49**	**40.56 ±0.46**
Diabetic +treated with *F. vulgare* 200mg	**Means ± SE**	**67.26 ±2.19**	**27.23 ±0.7**	**39.96 ±0.68**
Diabetic +treated with (*F. vulgare* 400mg + Propolis 400mg)	**Means ± SE**	**64.53 ±1.34**	**25.7 ±0.32**	**41.6 ±1.06**
Diabetic +treated with (*F. vulgare* 200mg + Propolis 200mg)	**Means ± SE**	**62.66 ±1.13**	**26.43 ±0.81**	**41.35 ±1.21**
Fratio		**1.14**	**2.119**	**1.427**
Probability		**N. S**	**N. S**	**N. S**

N. S=non-significant

Lymphocytes% shows a significant decrease (p<0.05) in Diabetic+treated with Propolis 200mg, Diabetic+treated with Propolis 400mg, Diabetic+treated with *F. vulgare* 400mg, Diabetic+treated with *F. vulgare* 200mg, Diabetic+treated with (*F. vulgare* 200mg+Propolis 200mg) and Diabetic+ treated with (*F. vulgare* 400mg+Propolis 400mg), when compared with Diabetic group (positive control) as shown in table (4) Where Mean and S. E was (81.53±**3.52**) in Diabetic group (positive control) and were (58.36±**1.9**), (**67.06±5.26**) in Diabetic+ treated with *F. vulgare*

200mg and Diabetic+treated with (*F. vulgare* 400mg+Propolis 400mg) respectively.

Monocytes % shows a significant increase ($p<0.05$) in Diabetic+treated with Propolis 400mg, Diabetic+treated with F. *vulgare* 200mg and Diabetic + treated with (*F. vulgare* 200mg+Propolis 200mg) when compared with Diabetic group (positive control) as shown in table (4) Where Mean and S. E was (9.53±**1.22**) in Diabetic group (positive control) and were (13.4±**0.34**), (**12.43**±2.01) in Diabetic+ treated with Propolis 400mg and Diabetic + treated with *F. vulgare* 200mg respectively. Diabetic+treated with *F. vulgare* 200mg, Diabetic+treated with (*F. vulgare* 200mg+Propolis 200mg) and Diabetic+ treated with (*F. vulgare* 400mg+Propolis 400mg) when compared with Diabetic group (positive control) as shown in table (4) Where Mean and S. E was (12.66±**0.84**) in Diabetic group (positive control) and were (29.2±**1.34**), (**22.16±3.96**) in Diabetic + treated with *F. vulgare* 200mg and Diabetic+treated with (*F. vulgare* 400mg+Propolis 400mg) respectively.

Table (4): The means ± standard error (SE) of differential (Lymphocyte, Monocyte and Neutrophil) % in induced-diabetic rats with Alloxan and treated with Propolis and *F. vulgare* doses for one month.

Parameters / Groups		Lymphocytes%	Monocytes%	Neutrophils%
Control (Non-Diabetic)	**Means ±SE**	**77.52a ±1.95**	**7.34a ±0.328**	**15.14ac ±2.03**
(positive control) (Diabetic)	**Means ± SE**	**81.53a ±3.52**	**9.53ab ±1.22**	**12.66a ±0.84**
Diabetic +treated with Propolis 200mg	**Means ± SE**	**60.72b ±1.73**	**11.6bc ±1.16**	**27.5b ±1.4**
Diabetic +treated with Propolis 400mg	**Means ±SE**	**59.26b ±4.01**	**13.4c ±0.34**	**27.33b ±3.87**
Diabetic +treated with *F. vulgare* 400mg	**Means ± SE**	**65.32b ±3.45**	**10.15bd ±2.41**	**24.52b ±2.6**
Diabetic +treated with *F. vulgare* 200mg	**Means ± SE**	**58.36b ±1.9**	**12.43cd ±2.01**	**29.2b ±1.34**
Diabetic +treated with (*F. vulgare* 400mg+Propolis 400mg)	**Means ± SE**	**67.06b ±5.26**	**10.76bc ±2.25**	**22.16cb ±3.96**
Diabetic +treated with (*F. vulgare* 00mg + Propolis 200mg)	**Means ± SE**	**59.53b ±4.77**	**12.96c ±2.49**	**28.13b ±4.03**
F. ratio		**7.307**	**5.67**	**5.72**
Probability		***	***	***

Mean with dissimilar superscriptletteraresignificantly different at ($p<0.001$)=***

Urea shows a significant decrease ($p<0.05$) in Control (Non Diabetic), Diabetic+treated with Propolis 200mg, Diabetic + treated with Propolis 400mg, Diabetic + treated with *F. vulgare* 400mg, Diabetic + treated with (*F. vulgare* 200mg+Propolis 200mg), Diabetic+treated with (*F. vulgare* 400mg+Propolis 400mg), when compared with Positive control (Diabetic) as shown in table (5) Where Mean and S. E was **(132±7.57)** in Positive control (Diabetic) and were **(36.6±3.57) and (75.25±18.09)** in Control (Non Diabetic) and Diabetic+ treated with *F. vulgare* 400mg respectively.

Creatinine shows a significant decrease ($p<0.05$) in Control (Non Diabetic), Diabetic+ treated with Propolis 200mg, Diabetic+treated with Propolis 400mg, Diabetic+treated with *F. vulgare* 200mg, Diabetic+treated with *F. vulgare* 400mg Diabetic+treated with (*F. vulgare* 200mg+Propolis 200mg), Diabetic+treated with (*F. vulgare* 400mg+Propolis 400mg), when compared with Positive control (Diabetic) as shown in table (5) Where Mean and S. E was **(0.91±0.16)** in Positive control (Diabetic) and were **(0.38±0.13) and (0.12±0.08)** in Diabetic+treated with Propolis 400mg and Diabetic+ treated with (*F. vulgare* 400mg+Propolis 400mg) respectively.

Table (5): The means± standard error (SE) of urea, creatinine and uricacid concentration in induced-diabetic rats with alloxan and treated with Propolis and *F. vulgare* doses for one month.

Parameters / Groups		Urea	Creatinine	Uricacid
Control (Non-Diabetic)	Means± SE	36.6±3.57a	0.31±0.05a	1.7±0.4
Positive control (Diabetic)	Means±SE	132±7.57b	0.91±0.16b	0.2±0.05
Diabetic +treated with Propolis 200mg	Means± SE	73.25±20.39a, c	0.18±0.04a	1.1±0.41
Diabetic +treated with Propolis 400mg	Means± SE	61.33±15.19a, c	0.38±0.13a	1.46±0.43
Diabetic +treated with *F. vulgare* 200mg	Means± SE	91±20.3c, b	0.2±0.07a	0.66±0.12
Diabetic +treated with *F. vulgare* 400mg	Means± SE	75.25±18.09c, d	0.37±0.18a	1.77±0.34
Diabetic +treated with (*F. vulgare* 200mg+Propolis 200mg)	Means± SE	47.33±13.38a, c	0.14±0.01a	0.9±0.05
Diabetic +treated with (*F. vulgare* 400mg+ Propolis 400mg)	Means± SE	41.33±4.97a, d	0.12±0.08a	1.23±0.58
Fratio		4.43	4.7	1.96
Probability		**	**	N. S.

Mean with dissimilar superscript letter are significantly different at (P<0.05); N. S =non-significant (p<0.001)=**

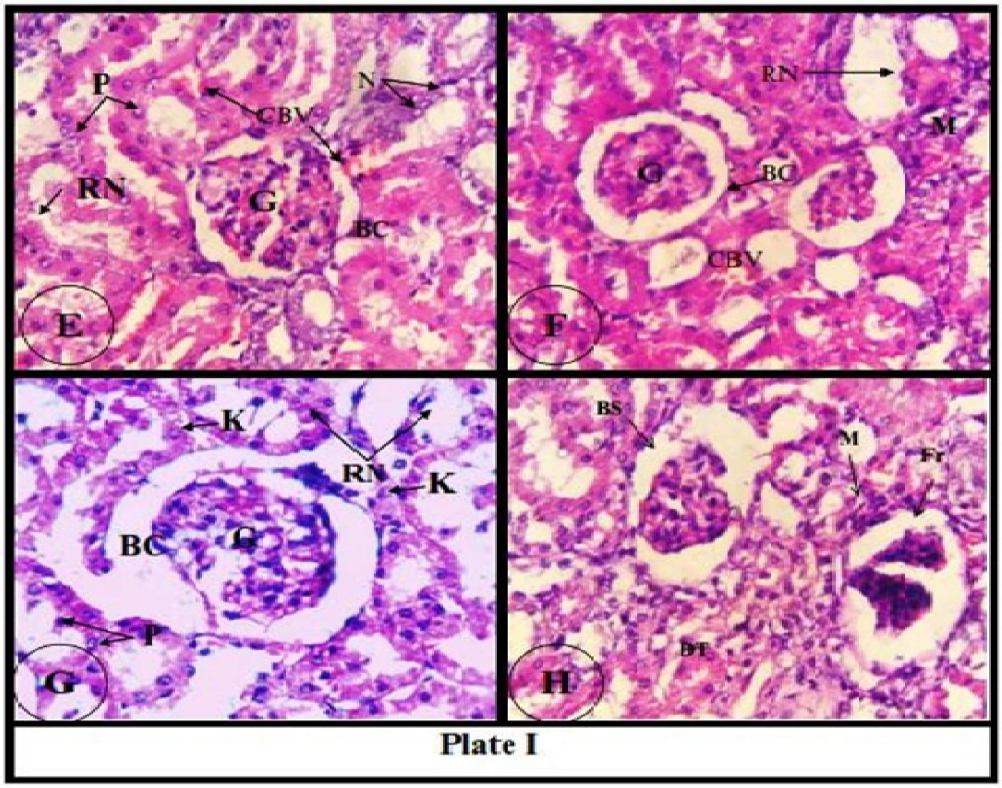

Plate I

Plate I: (E): Enlarged transverse section of kidney of adult diabetic albino rat treated with 200mg of *Foeniculum vulgare* showed normal glomerular (G), mildly congested blood vessels (CBV), improved Bow man's capsule (BC), atrophy and dilated of renal tubules (RN) with attenuation of Necrosis (N) and Pyknosis (P). (H & E x400).

(F): Enlarged transverse section of kidney of adult diabetic albino rat treated with 400 mg of *Foeniculum vulgare* + 400 mg of propolis showed abnormal glomerular (G), mildly congested blood vessels (CBV), degenerations of renal tubules (RN) and with inflammatory cells (M) (H & Ex400).

(G): Enlarged transverse section of kidney of adult diabetic albino rat treated with 200 mg of *Foeniculum vulgare*+ 200 mg of propolis showed abnormal architecture of the kidney represented by degenerations of glomerular (G), renal tubules (RN) and Bowman's capsule (BC) and renal tubules with multipyknotic (P) and karyorrhexis (K) nucleoli (H & Ex400).

(H): Enlarged transverse section of kidney of adult diabetic albino rat treated with 200mg of Propolis showed degeneration of renal tubules (RN), shrinkage with fragmentation of glomeruli (G), aggregation of inflammatory cells (M), and pyknosis (P) in some renal tubular cells were noticed. (H & Ex400).

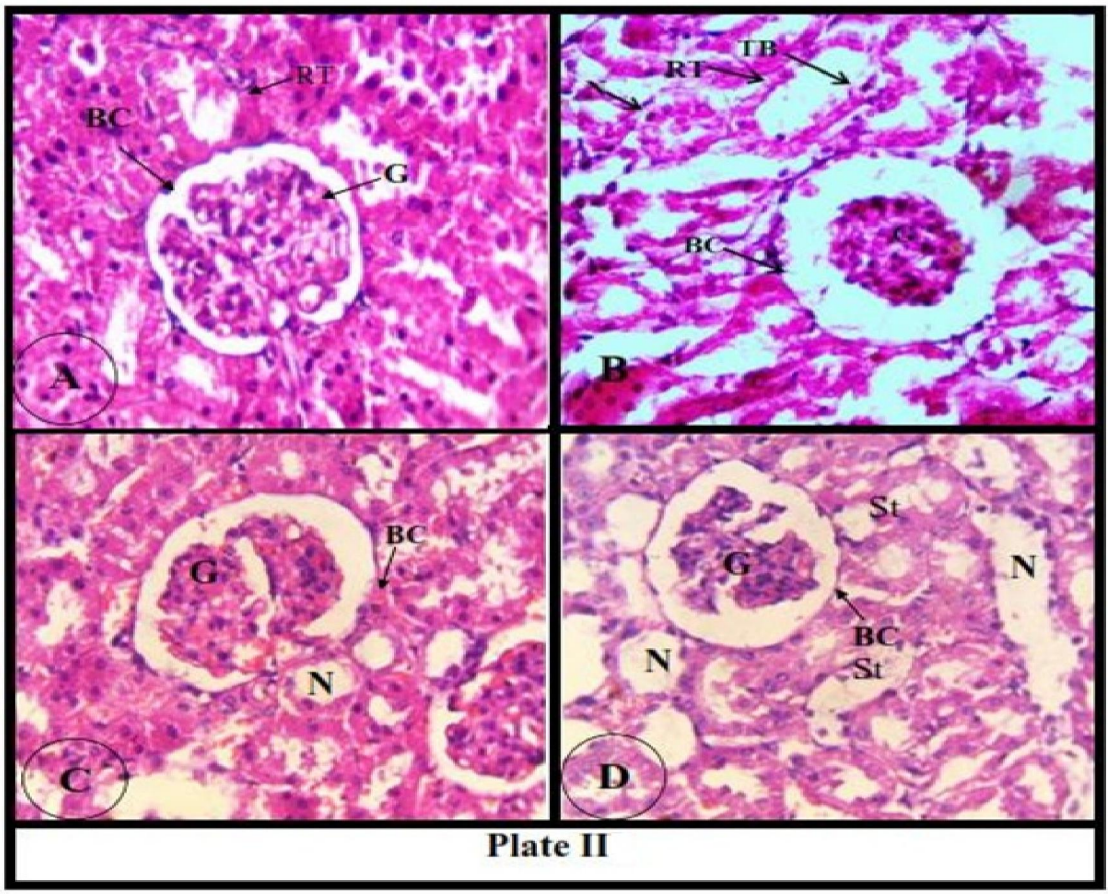

Plate II: **(A):** Enlarged Transverse section in normal kidney structure of adult albin or at, showed normal Bowman's capsule (BC), glomeruli (G), renal tubules (RT) and distal tubules (DT) (H & Ex400).
(B): Enlarged transverse section of kidney of adult diabetic albino rat showed degenerations of glomerular (G), abnormal renal tubules (RN) represented by multi necrotic tubules (N), tubular brush borderloss (TB) and degenerations of Bowman's capsule (BC) with varying space between the Bowman's capsule and glomerulus. (H & Ex400).
(C): Enlarged transverse section of kidney of adult diabetic albino rat treated with400 mg of Propolis showed normal architecture of the kidney glomerulus (G), Renal tubules (RN) appeared to be regenerated and necrotic cells (N) also appear. (H & E x400).
(D): Enlarged transverse section of kidney of adult diabetic albino rat treated with400 mg of *Foeniculum vulgare* showed normal glomerulus (G) with short space between the Bowman's capsule and glomeruolus, abnormal renal tubules (RN) represented by multi necrotictubules (N) and Steatosis (St). (H & Ex400).

4. Discussion

1-Hematological parameters:

The Alloxan is one of the chemical agents, which are used to induce diabetes mellitus experimentally. Its mechanism in inducing diabetesis the partial destruction of the β-cells of islets of Langerhans **(Szkudelski,2001).** The alloxan is selectively taken up into the β-cells by a glucose transporter (GLUT2) **(Gorus *et al.*,1982).** In addition, hyperglycemia occurs due to the defects in the liver and skelet al muscle glycogen storage and inability of the tissues to take up and utilize glucose **(Lamba *et al.*, 2000).**

The alloxan is a chemical compound which is used to induce diabetes mellitus through inducing diabetes by partial destruction of the beta cells of islets of Langerhans **(Szkudelski, 2001)**. Lambda et al., 2000 reported that alloxan cause hyperglycemia through induction defects in the liver and skeletal muscle glycogen storage and inability of the tissues to take up and utilize glucose.

1. Red blood corpuscles (R. B. C. s)

Regarding to the results of RBCs, it shows a significant increase ($p<0.05$) in Control (Non Diabetic), Diabetic+ treated with Propolis 200mg, Diabetic+ treated with *F. vulgare* 400mg,

Diabetic+treated with *F. vulgare* 200mg, Diabetic+treated with (*F. vulgare* 400mg+Proplis 400mg) when compared with Positive control (Diabetic) this is may be due to increase in free radical generation, decreased antioxidant defenses, and oxidative modifications of the membrane increase fragility of RBCs. These mechanismsled to anemia and consequent depletion of endogenous antioxidant reserves **(Abdul-Hadi, 2014).** In particular, reactive O2 species generated during Alloxan metabolism is implicated in red cell damage **(Rao *et al.*,2003).**

2. White blood cells (W. B. C. s)

The results show a significant decrease ($p<0.05$) in Control (Non Diabetic), Diabetic+treated with Propolis 200mg, Diabetic +treated with *F. vulgare* 400mg, Diabetic+treated with *F. vulgare* 200mg, Diabetic + treated with (*F. vulgare* 200mg+Propolis 200mg), when compared with Positive control (Diabetic) and this is may be due to increase inflammation which caused by Alloxan this results disagreements with **(Abdul-Hadi, 2014)** which suggested that decreased hemopoietic activity reduced rate of WBCs release from the bone marrow to blood.

Regarding to the results of numbers oftotal WBCs were significantly improved at Diabetic + treated with Propolis 200mg, Diabetic+treated with *F. vulgare* 400mg, Diabetic+treated with *F. vulgare* 200mg, Diabetic + treated with (*F. vulgare* 200mg+Propolis 200mg), when compared with Positive control (Diabetic). According to **Orsolić and Basic (2005)**, Propolis increased the proliferation of leukocyte precursors from pluripotent stem cells. Furthermore, prolonged administration of Propolis elevated the myeloidandmega karyocytictype of colony forming units.

3. Haemoglobin concentration (Hb)

Regarding to the results of Hb, it shows a significant increase ($p<0.05$) in Control (Non Diabetic), Diabetic+ treated with Propolis 200mg, Diabetic+treated with Propolis 400mg, Diabetic+treated with *F. vulgare* 400mg, Diabetic+treated with *F. vulgare* 200mg, Diabetic+treated with (*F. vulg*are 400mg+Proplis 400mg), Diabetic + treated with (*F. vulgare* 200mg+Proplis 200mg) when compared with Positive control (Diabetic). The results of this study demonstrated that alloxan resulted in a significant decreased in Hb concentration. The decrease in Hb content in diabetic rats suggests the direct effect of the excess glucose present in blood. Previous studies demonstrated that during diabetes the excess glucose present in blood reacts with hemoglobin to form glycosylated hemoglobin. So, the total hemoglobin level is decreased in Alloxan diabetic animals **(Sheela and Augusti, 1992 and Luo *et al.*, 2004).** Moreover, propolis improves the digestive utilization of ironand increases the regeneration efficiency of hemoglobin especially during recovery from ananaemic syndrome **(Haro *et al.*, 2000).**

4. Haematocrit (Hct)

Hctrepresents the percentage of erythrocytes to blood plasma. Therefore, the decrease in the number of erythrocytes leads to adeclinein the value of Hct.

Regarding to the results of Hct, it shows a significant increase ($p<0.05$) in Control (Non Diabetic), Diabetic+ treated with Propolis 200mg, Diabetic+treated with Propolis 400mg, Diabetic + treated with *F. vulgare* 400mg, Diabetic+ treated with *F. vulgare* 200mg, Diabetic + treated with (*F. vulgare).*

400mg+Propolis 400mg), Diabetic + treated with (*F. vulgare* 200mg+Proplis 200mg) when compared with Positive control (Diabetic) maybe resulted from the toxic effect of alloxan used to induce diabetes in these animals. Similar result recorded in rats **(Helal *et al.*, 2005)** and in rabbits **(Abdul-Hadi, 2014)**.

Kidney function

Kidney functions include creatinine, urea and uricacid. Serum levels of creatinine, ametabolicby product of creatine that supplies energy for muscle contraction and urea, generated in the liver by metabolized protein are markers of optimal renal function. Elevated levels of the semetabolites signify impairment in kidney function **(Shokeen, *et al.*, 2008).**

Creatinine

Regarding to the results of creatinine, it shows a significant decrease ($p<0.05$) in Control (Non Diabetic), Diabetic +treated with Propolis 200mg, Diabetic+treated with Propolis 400mg, Diabetic+treated with *F. vulgare* 200mg, Diabetic+ treated with *F. vulgare* 400mg Diabetic +treated with (*F. vulgare* 200mg+Propolis 200mg), Diabetic+treated with (*F. vulgare* 400mg+Propolis 400mg), when compared with Positive control (Diabetic) this is may be due to nephrotoxicity. This result Agreements with **(Amin *et al.*,2013).**

Urea

Diabetic nephritis is one of the common complications of diabetes mellitus since the high level blood glucose always put a heavy burden on their kidney. Asamain renal function indicator **(Sabu *and Kuttan*, 2002).** Regarding to the results of urea, it shows a significant decrease ($p<0.05$) in Control (Non Diabetic), Diabetic+ treated with Propolis 200mg, Diabetic +treated with Propolis 400mg, Diabetic+treated with *F. vulgare* 400mg, Diabetic+treated with (*F. vulgare* 200mg+Propolis 200mg), Diabetic+treated with (*F. vulgare* 400mg+Propolis 400mg), when compared with Positive control (Diabetic) this is maybe due to increase metabolism of protein. These results are in agreement with **(Liu *et al.*, 2009).**

The effect on the kidney tissues

The microscopic appearance of kidney of Alloxan induced diabetic rat showed degenerations of glomeruli, abnormal renal tubules represented by multi necrotic tubules, tubular brush border loss and degenerations of Bowman's capsule with varying space between the Bowman's capsule and glomeruli.. According to **Yanardag *et al.* (2002)** the treatment of rats with Alloxan showed some histopathological changes in the kidney in the form of degeneration, inflammation, necrosis, mesangialhypercellularity and deformed renal tissue architecture. Also, **Selvan *et al.* (2008)** reported that the kidney in diabetic rats showed degenerative changes in cortex, medulla and necrosis of tubules. In addition **de Zeeuw *et al.* (2006)** observed that in diabetics, the kidney sections showed damaged glomeruli, proximal tubules and interstitial inflammation.

Conclusion:

1- Propolis and *Foeniculum vulgar* increases RBCs count and decrease WBCs count.

2- Propolis and *Foeniculum vulgar* increase hemoglobin content and HCT%.

3- Lymphocytes decreases by propolis and *Foeniculum vulgar* and also neutrophils but monocytes increases.

4- Both ameliorates destructive effects of diabetes on kidneys tissues specially on glomeruoli and Bowman's capsule.

Recommendation

We recommend with using both propolis and *Feoniculumvolger* in case of diabetis to improve RBCs count and hemoglobin and also improve kidney functions due to antioxidant activity.

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