

Antioxidants and Hypoglycemic Studies on Egyptian Propolis and *Foeniculum Vulgare* on Alloxan Induced Diabetic Rats

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Abstract

Background: Diabetes Mellitus (DM) is one of the leading causes of death, illness, and economic loss in the Egypt. In DM the oxidative stress exceeds the body's antioxidant defense mechanisms. Although oxidative stress and free radicals have been reported to play a significant role in diabetic complications. Propolis and *Foeniculum vulgare* (fennel) possesses antioxidant and anti-diabetic activities. **Aim of work:** This study was carried out to evaluate the effect of Egyptian propolis and *Foeniculum Vulgare* on hyperglycemia-induced oxidative stress in diabetic rats. **Materials and methods:** Diabetes was induced with Alloxan (148mg/Kg) intraperitoneal. Rats with blood glucose level less than 300 mg/dL were excluded. Animals were divided into 8 equal groups (n=80); except negative control rats, all groups inoculated with alloxan Group 1: negative control of normal rats. Group 2: positive control of alloxan injected rats. Group 3: rats were treated with 200 mg/ kg of propolis. Group 4: rats were treated with 400 mg/ kg of propolis. Group 5: rats were treated with 200 mg/ kg of *Foeniculum vulgare*. Group 6: rats were treated with 400 mg/ kg of *Foeniculum vulgare*. Group 7: rats were treated with (200 mg/ kg of *Foeniculum vulgare* +200 mg/ kg of propolis). Group 8: rats were treated with (400 mg/ kg of *Foeniculum vulgare* +400 mg/ kg of propolis). Rats were treated orally for 28 days. **Results:** Data showed significant increase in serum levels of Fasting blood glucose FBG, malonaldehyde MDA, superoxide dismutase SOD and significant decreased levels of insulin, Catalase, glutathione (GSH) reduce, glutathione -S- transferase (GST) were observed in the diabetic untreated animals. **Conclusion:** Propolis and *Foeniculum Vulgare* possesses hypoglycemic activities in addition to its ability to ameliorate oxidative stress induced organ dysfunction.

Keywords

Diabetes, Propolis, *Foeniculum Vulgare*, Alloxan, Hyperglycemia, Oxidative Stress

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1. Introduction

Diabetes mellitus (DM) is a chronic disease caused by inherited or acquired deficiency in production of insulin by beta cells of pancreas, or by the ineffectiveness of the insulin. It is an extremely common metabolic disorder affecting carbohydrate, fat and protein metabolism characterized by hyperglycemia, glucose urea and negative nitrogen balance. It is mainly due to lack of insulin secretion, or resistance to

insulin action or both (Boddupalli *et al.*, 2012). It is the most prevalent disease in the world affecting 25% of population and afflicts 150 million People and is set to rise to 300 million by 2025. The disease takes an ever-increasing proportion of national and international health care budgets. It is projected to become one of the world's main disablers and killers within the next 25 years. Regions with greatest

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potential are Asia and Africa (Osadebe *et al.*, 2014). Diabetes Mellitus is one of the leading causes of death, illness, and economic loss in the United States (A.D.A., 2008).

One of the potent methods employed in inducing diabetes in experimental animals is by the use of Alloxan (Etuk, 2010), as it has been found to selectively destroy the insulin-producing β -cells of the pancreas by oxidation of essential sulfhydryl (-SH groups), inhibition of glucokinase enzyme, generation of free radicals and disturbances in intracellular calcium homeostasis (Szkudelski, 2001; Dhanesha *et al.*, 2012). Hyperglycemia increases in the level of reactive oxygen species causes autooxidative glycosylation of cell membranes, destruction of the antioxidant systems, lipid peroxidation, and tissue injury (Amin *et al.*, 2013; Baynes, 1991). The use of alloxan has been found to mimic the oxidative stress status experienced by diabetic patients.

Alloxan is a hydrophilic and unstable substance. Its half-life at neutral pH and 37°C is about 1.5 min and is longer at lower temperatures (Lenzen, 2008). Alloxan has been used to induce diabetes in experimental animals. Alloxan produces oxygen radicals in the body which can cause injury of pancreas (Halliwell and Gutteridge, 1999) that is responsible for increased blood glucose in animals. The action of alloxan in the pancreas is preceded by its rapid uptake by the β cells which has been proposed to be one of the important features determining alloxan diabetogenicity. A similar uptake of alloxan also takes place in the liver. However, the liver and other tissues are more resistant to reactive oxygen species in comparison to pancreatic β cells and this resistance protects them against alloxan toxicity. Another aspect concerns the formation of reactive oxygen species that is preceded by alloxan reduction. In β cells of the pancreas its reduction occurs in the presence of different reducing agents. Since alloxan exhibits a high affinity to the SH-containing cellular compounds, reduced glutathione (GSH), cysteine and protein-bound sulfhydryl groups (including SH containing enzymes) are very susceptible to its action. Alloxan and the product of its reduction, dialuric acid, establish a redox cycle with the formation of superoxide radicals. These radicals undergo dismutation to hydrogen peroxide. Thereafter highly reactive hydroxyl radicals are formed by the Fenton reaction. The action of reactive oxygen species with a simultaneous massive increase in cytosolic calcium concentration causes rapid destruction of β cells (Szkudelski, 2001).

Hyperglycemia is an important factor responsible for the intense oxidative stress in diabetes, and the toxicity induced by glucose autooxidation is likely to be one of the important sources of reactive oxygen species (Giugliano *et al.*, 1996). Additionally, lipid peroxidation plays an important role in the production of free radicals and oxidative stress in diabetes (Halliwell, and Gutteridge, 1994). Several intra- and

extracellular antioxidant defense mechanisms counteract the destructive effects of free radicals by attenuating or omitting their activities (Afshari *et al.*, 2007). However, in DM the oxidative stress exceeds the body's antioxidant defense mechanisms. Although oxidative stress and free radicals have been reported to play a significant role in diabetic complications (Hamada *et al.*, 2009) and treatment with antioxidants has been reported to reduce these complications, (Yilmaz *et al.*, 2004). Recent studies have shown that propolis has hypoglycemic, hypolipidemic, and antioxidant 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 has also been reported to enhance the antioxidant defense system (Matsui *et al.*, 2004) and to protect pancreatic tissue (El-Sayed *et al.*, 2009).

Propolis of different geographical regions have been found to possess several biological activities, among which its oxygen radical scavenging activity (Chen *et al.*, 2004).

As 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 sticky, resinous substance collected by honey bees from the sap, leaves, and buds of plants, and then mixed with secreted beeswax. Propolis has been used as a folk medicine in many countries from ancient times (Ahuja, V. and Ahuja, A. 2011). Propolis, a natural product is a resinous substance that honey bees (*Apis mellifera*) collect from tree buds, shrubs or other botanical sources. The main chemical classes present in propolis are flavonoids, phenolics and other various aromatic compounds and has been used extensively in folk medicine due to its several pharmacological properties (Abdul-Hadi, 2014).

It has been characterized variously as an anti-bacterial, anti-viral, anti-inflammatory, anti-oxidant, and anti-carcinogenesis agent. Though bees use propolis to reinforce their hive walls and protect the hives from infection, humans use these products to boost their immune system (Koya-Miyata, *et al.*, 2009). Propolis is a resin widely used in folk medicine for centuries. The Egyptians used propolis, honey and other resins to mummify their pharaohs preserving them, as far as possible, for the next life. Propolis has been used by man since these times in one form or another to stay well and to treat disease. It is known that propolis exhibits several pharmacological properties such as antimicrobial, anti-inflammatory, healing, anesthetic, cytostatic and cariostatic properties. In China, propolis was authorized as a new material medicine and embodied in the Chinese pharmacopeia in 2005 (Zhu, *et al.* 2010).

(Hanan and Nareman, 2015): Reported that treatment of diabetic rats with propolis induced significant decrease of fasting blood glucose levels.

(Mhaidat, *et al.*, 2015) concluded that *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 *F. vulgare* extract might be potential future herbal remedy for diabetes and its complications. (Mostafa, *et al.*, 2015) reported that *Foeniculum vulgare* Mill, family Umbelliferae, is well known for its essential oil. One of the major components of *Foeniculum vulgare* seed's essential oil is trans anethole. *Foeniculum vulgare* (fennel) possesses antioxidant and anti-diabetic activities.

2. Materials and Methods

2.1. Experimental Animals

The 80 male albino rats (*Rattus rattus*) at average weight of (190±10) at the beginning of the experimental. Obtained from the Egyptian holding company for biological product and Vaccines were used as experimental animals.

2.2. 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 diabetic state was determined 72 hours after alloxan administration through the tail, using the one touch ultra-glucometer (Glucodector). Weekly record of blood glucose level was taken afterwards.

2.2.1. Propolis

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

2.2.2. Form of the Agent

Bulk of glue like brownish material resulted from scrapping off the frames of bee hives.

2.2.3. Preparation

Propolis bulks were cut into small pieces and mixed with deionized water and shaken at 95 °C for 2 hours according to therapeutic dose. Then cooled to room temperature and centrifuged at 1500 revolution per minute (r.p.m) for 5 minutes to obtain the supernatant (El-Akabawy *et al.* 2004). This occurs in genetic engineering center Al-azhar University.

2.2.4. Foeniculum Vulgare

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

microscopically characters

2.2.5. Preparation

Foeniculum vulgare extracted by distilled water using soxhlet apparatus in physiology lab faculty of science al Azhar University.

2.3. Experimental Design

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

Group 1 Control (C): negative control of normal rats, (n=10 Rats) rats of this group were neither treated nor injected by alloxan. Group 2 Diabetes Mellitus (DM): positive control of alloxan injected rats, (n=10 Rats) rats of this group were injected by alloxan 148 mg/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 200 mg/ kg of propolis. Group 4 Diabetes Mellitus+ 400 propolis (DM+400Pro): Rats of this group were injected with alloxan 148 mg/kg intraperitoneal and treated with 400 mg/ kg of propolis. Group 5 Diabetes Mellitus + 200 *Foeniculum vulgare* (DM+200FV): Rats of this group were injected with alloxan 148 mg/kg intraperitoneal and treated with 200 mg/ 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 400 mg/ kg of *Foeniculum vulgare*. Group 7 Diabetes Mellitus+200 propolis + 200 *Foeniculum vulgare* (DM+200Pro+200FV): Rats of this group were injected with alloxan 148 mg/kg intraperitoneal and treated with (200 mg/ kg of *Foeniculum vulgare*+ 200 mg/ kg of propolis). Group 8 Diabetes Mellitus+400 propolis + 400 *Foeniculum vulgare* (DM+400Pro+400FV): Rats of this group were injected with alloxan 148 mg/kg intraperitoneal and treated with (400 mg/ kg of *Foeniculum vulgare*+ 400 mg/ kg of propolis).

2.4. Preparation of Tissue Homogenate

After the animals have been sacrificed, livers were quickly excised, placed in chilled phosphate buffer solution (pH 7.4) at 4°C, One gram of liver then is taken to prepare 10% tissue homogenate using the same buffer solution utilizing tissue homogenizer (Bhattacharyya, 2003) The homogenates were centrifuged in a cooling centrifuge with a temperature adjusted to +4°C, at 4,000 rpm for 10 min. The supernatants obtained were transferred into eppendorf tubes, and preserved at -80°C in a deep freezer until used for analysis of antioxidant biomarker.

2.4.1. Biochemical Analysis

Determination of serum glucose (mg/dl): Serum blood

glucose was determined according to the method of Dods (2003) using kit from Elitech diagnostic Co. France.

Determination of serum Insulin level mIU/l: serum insulin was estimated according to the enzyme linked immune sorbent assay “ELISA” micro plate method described by Eastham (1985) using the Kits of Diagnostic Automation, Inc.

2.4.2. Lipid Peroxidation

Determination of thiobarbituric acid reactive substances (TBARS) level of liver tissue:

The level of TBARS was determined according to the method of (Yoshioka *et al.*, 1979). The method is based on the determination of the malondialdehyde (MDA) an end product of lipid peroxidation, which can react with thiobarbituric acid (TBA) in acidic medium at temperature of 95°C for 30 minutes to form thiobarbituric acid reactive product.

Estimation of superoxide dismutase (SOD) enzyme activity of liver tissue (Unit/mg wet tissue): The level of SOD activity was determined in hepatic homogenate according to the method described by (Marklund and Marklund, 1974).

Determination of hepatic (CAT) enzyme activity of liver tissue (Unit/g wet tissue): Catalase activity of the tissue homogenate was determined according to the method of Aebi (1984). The assay was performed according to the instruction manual of reagent kits purchased from Biodiagnostic Co., Dokki, and Giza, Egypt.

Evaluation of liver GST level (U/g tissue): Glutathione-S-transferase activity of the tissue homogenate was determined according to the method of Habig *et al.* (1974). The assay was performed according to the instruction manual of reagent kits purchased from Biodiagnostic Co., Dokki, and Giza, Egypt.

Determination of Hepatic Reduced Glutathione (GSH) (m mole/gm wet tissue): The assay of GSH activity was determined according to the method of Beutler *et al.* (1963) using commercial kit purchased from Bio-diagnostics Company Egypt.

2.4.3. Statistical Analysis

The values were expressed as mean \pm S.E. Statistical analysis was performed by one way analysis of variance (ANOVA) followed by lest significant different (LSD) using SPSS 20 for Windows 7.

3. Results

Fasting blood glucose FBG shows a significant decrease ($p<0.05$) in C., D.M. +200pro, D.M. +400pro, D.M. +200F.v, D.M. + 400F.v, D.M. + 200pro + 200F.v, D.M. + 400pro + 400F.v. when compared with Positive control (Diabetics) as in table 1 & fig. 1 Where Mean and S.E was (538.67 \pm 49.46) in Positive control (Diabetics) and were (85.67 \pm 2.33), (156.5 \pm 13.45), (182.33 \pm 15.92), (287.67 \pm 9.83), (180.25 \pm 17.31), (175.67 \pm 2.96), and (123 \pm 3.78) respectively.

Table 1. Shows the mean \pm SE of F.B.G, Insulin, MDA, SOD, GSH Trans, GSH red and Catalase concentration in rats subjected to alloxan and treated with Propolis & *F.volgure* doses for one month.

Parameters		F.B.G	Insulin	MDA	SOD	GST	GSH	Catalase
Groups								
C	Means \pm SE	85.67 \pm 2.33a	2.14 \pm 0.097a	195.20 \pm 7.26a,c	69.6 \pm 1.5a	1.04 \pm 0.05a	3.4 \pm 0.24a	1.45 \pm 0.07a
Non diabetic								
P.C	Means \pm SE	538.67 \pm 49.46b	0.25 \pm 0.032b	551.77 \pm 17.01b	157.45 \pm 11.98b	0.47 \pm 0.01b	1.07 \pm 0.1b	0.61 \pm 0.04b
Diabetic								
D+200P	Means \pm SE	156.5 \pm 13.45c,e	1.48 \pm 0.048f	174.3 \pm 19.29a	99.22 \pm 5.34a,c	0.65 \pm 0.09b,c	3.28 \pm 0.89a	0.75 \pm 0.08b,c
D+400P	Means \pm SE	182.33 \pm 15.92c,e	1.27 \pm 0.081c	178.33 \pm 8.33a	88.69 \pm 2.17a,c	0.56 \pm 0.08b,c	1.34 \pm 0.3b	0.95 \pm 0.06c,d
D+200 F.v.	Means \pm SE	287.67 \pm 9.83d	0.53 \pm 0.044e	251.77 \pm 38.54c	114.4 \pm 36.07c	0.75 \pm 0.13c	2.47 \pm 0.22a,b	1.09 \pm 0.09d
D+400 F.v.	Means \pm SE	180.25 \pm 17.31e	0.905 \pm 0.027d	220.98 \pm 28.19a,c	125.37 \pm 2.7c,b	0.69 \pm 0.04b,c	2.6 \pm 0.72a,b	1.44 \pm 0.04a
D+ (200P+200 F.v.)	Means \pm SE	175.67 \pm 2.96c,e	0.98 \pm 0.035d	188.3 \pm 16.54a,c	99.84 \pm 6.41a,c	0.6 \pm 0.03b,c	1.47 \pm 0.25b	1.04 \pm 0.08d
D+ (400P+400 F.v.)	Means \pm SE	123 \pm 3.78a,c	1.61 \pm 0.06f	252.21 \pm 13.51c	105.45 \pm 16.58c	0.6 \pm 0.11b,c	3.85 \pm 0.96a	1.15 \pm 0.18d
F ratio		48.871	88.11	33.69	4.5	5.77	3.024	12.124
Probability		***	***	***	**	***	*	***

Mean with dissimilar superscript letter are significantly different at ($P<0.05$) ($p<0.05$) =* ($p<0.01$) =** ($p<0.001$) =***

Malondialdehyde (MDA) shows a significant decrease ($p<0.05$) in C., D.M. +200pro, D.M. +400pro, D.M. +200F.v, D.M. + 400F.v, D.M. + 200pro + 200F.v, D.M. + 400pro + 400F.v. when compared with Positive control (Diabetics) as

in table 1 & fig. 3 Where Mean and S.E was (551.77 \pm 17.01) in Positive control (Diabetics) and were (195.2 \pm 7.26), (174.3 \pm 19.29) and (252.21 \pm 13.51) in C., D.M. +200pro, D.M. + 400pro + 400F.v. respectively.

Superoxide dismutase (SOD) shows a significant decrease ($p<0.05$) in C., D.M. +200pro, D.M. +400pro, D.M. +200F.v, D.M. + 200pro + 200F.v, D.M. + 400pro + 400F.v. when compared with Positive control (Diabetics) as in table 1 & fig. 4 Where Mean and S.E was (157.45 ± 11.98) in Positive control (Diabetics) and were (69.6 ± 1.5) and (105.45 ± 16.58) in C., and D.M. +400pro+400 F.v. respectively.

Insulin shows a significant increase ($p<0.05$) in C., D.M. +200pro, D.M. +400pro, D.M. +200F.v, D.M. + 400F.v, D.M. + 200pro + 200F.v, D.M. + 400pro + 400F.v. when compared with Positive control (Diabetics) as in table 1 & fig. 2 Where Mean and S.E was (0.25 ± 0.032) in Positive control (Diabetics) and were (2.14 ± 0.097) and (0.53 ± 0.044) in C., and D.M. +200 F.v. respectively.

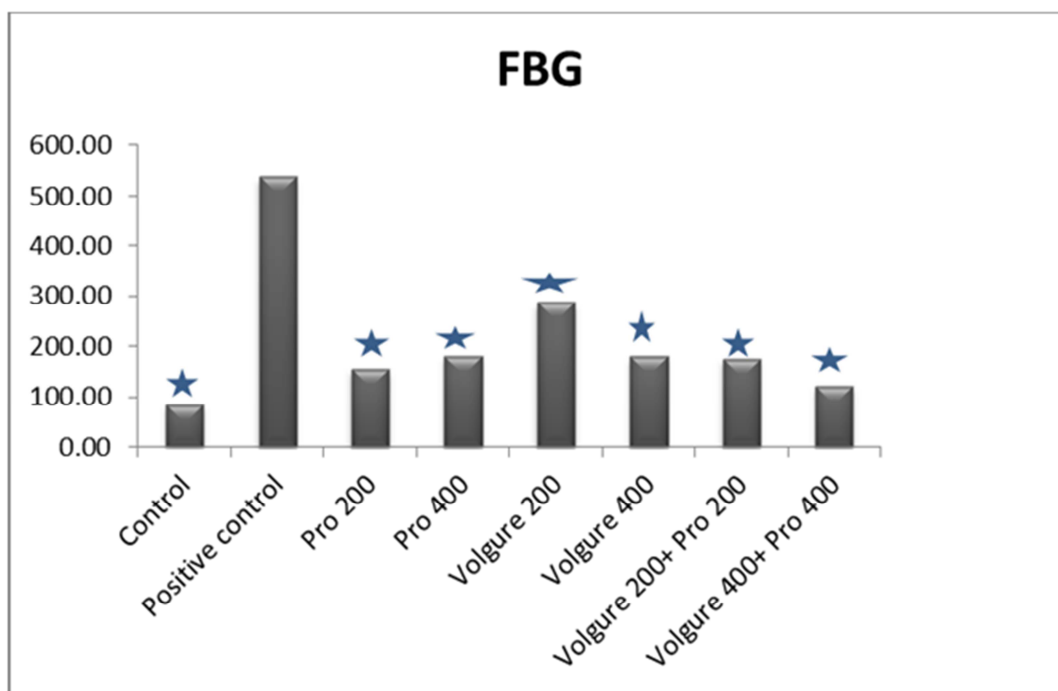


Fig. 1. Shows the mean of Fasting blood glucose concentration in rats subjected to alloxan and treated with Propolis & *F. vulgare* doses for one month.

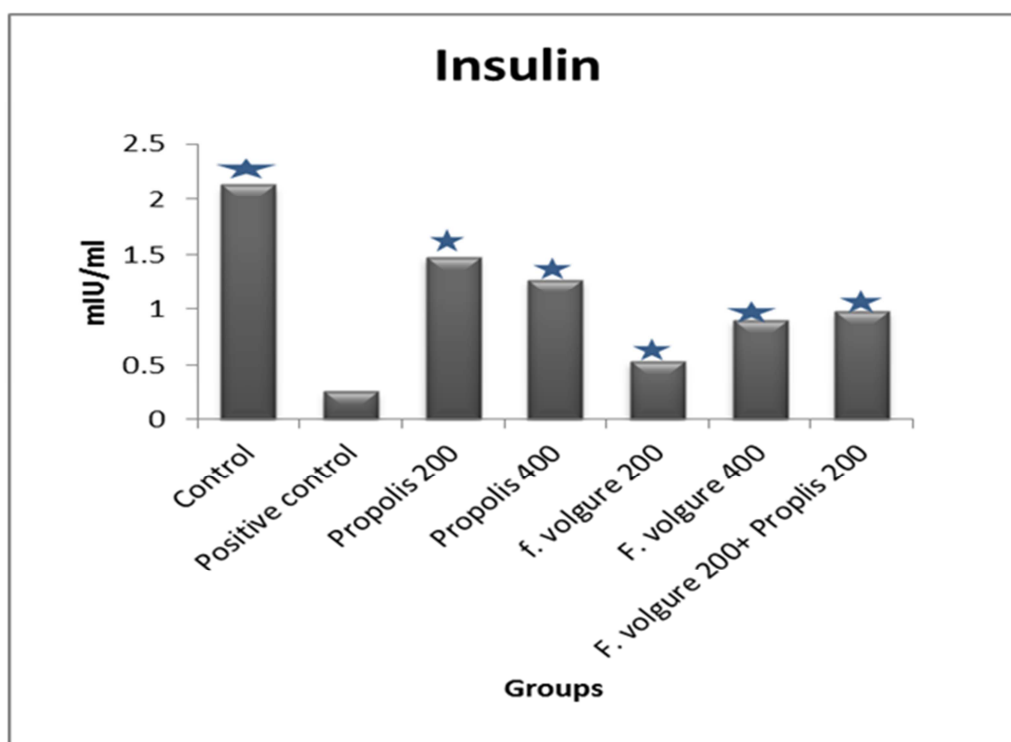


Fig. 2. Shows the mean of Insulin concentration in rats subjected to alloxan and treated with Propolis & *F. vulgare* doses for one month.

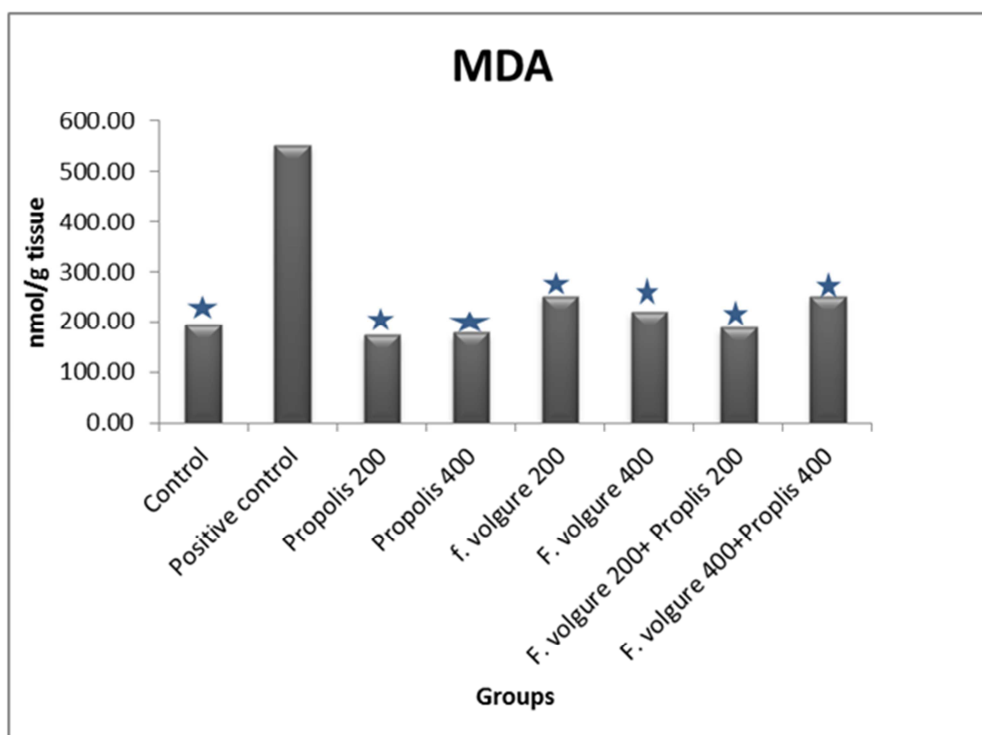


Fig. 3. Shows the mean of Malondialdehyde concentration in rats subjected to alloxan and treated with Propolis & *F.vulgare* doses for one month.

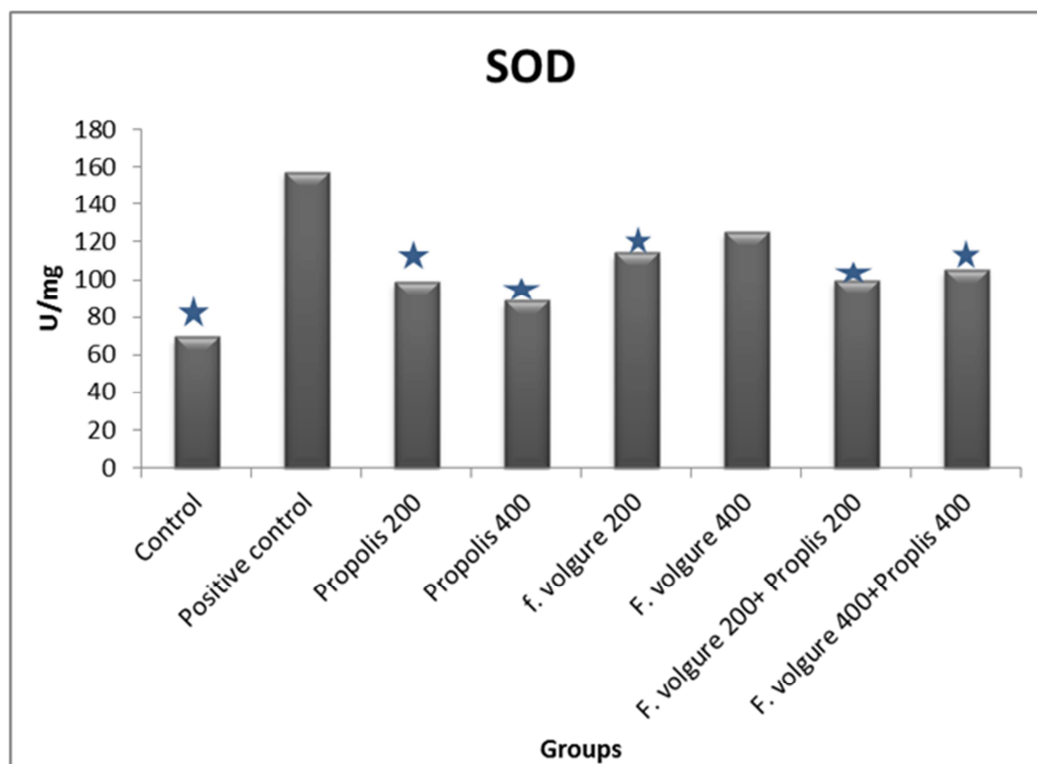


Fig. 4. Shows the mean of Superoxide dismutase concentration in rats subjected to alloxan and treated with Propolis & *F. vulgare* doses for one month.

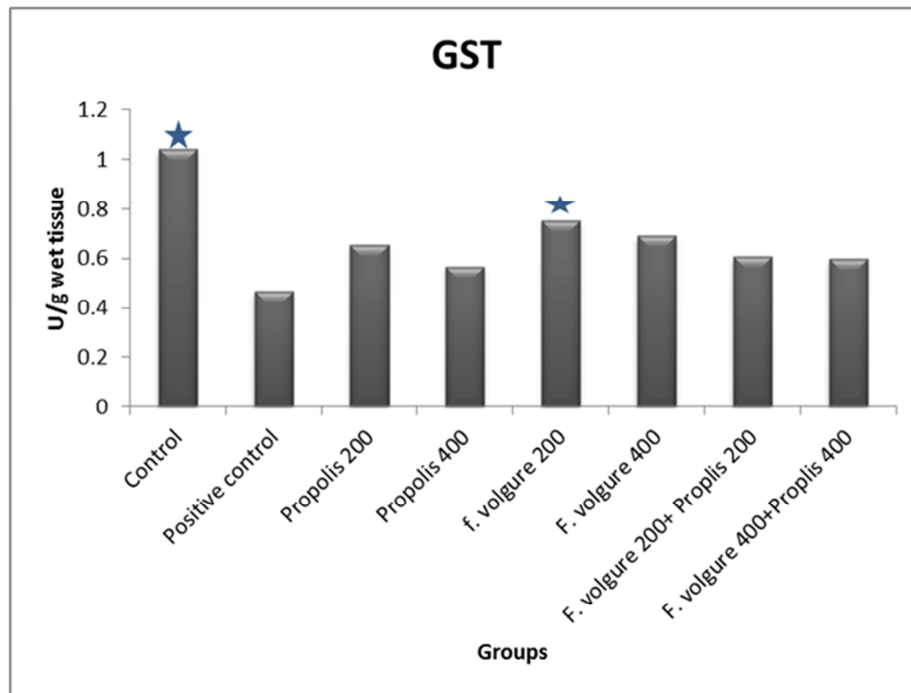


Fig. 5. Shows the mean of GST concentration in rats subjected to alloxan and treated with Propolis & *F. vulgare* doses for one month.

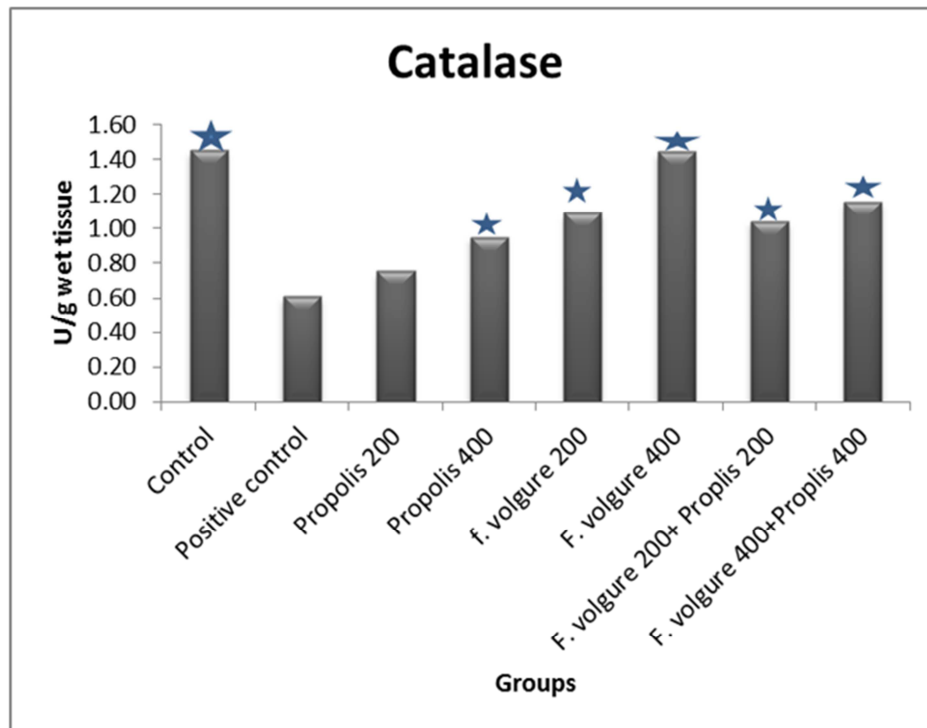


Fig. 6. Shows the mean of catalase concentration in rats subjected to alloxan and treated with Propolis & *F. vulgare* doses for one month.

Glutathione-S-transferase (GST). Shows a significant increase ($p < 0.05$) in C., and D.M. + 200 F.v. when compared with Positive control (Diabetics) as in table 1 & fig. 5 Where Mean and S.E was (0.47 ± 0.01) in Positive control (Diabetics) and were (1.04 ± 0.05) and (0.75 ± 0.13) in C., and D.M. + 200 F.v. respectively.

Hepatic Reduced Glutathione (GSH). Shows a significant increase ($p < 0.05$) in C., D.M. + 200pro, D.M. + 400pro + 400F.v. when compared with Positive control (Diabetics) as in table 1 & fig. 7 Where Mean and S.E was (1.07 ± 0.1) in Positive control (Diabetics) and were (3.4 ± 0.24) , (3.28 ± 0.89) and (3.85 ± 0.96) in C., and D.M. + 400pro + 400F.v. respectively.

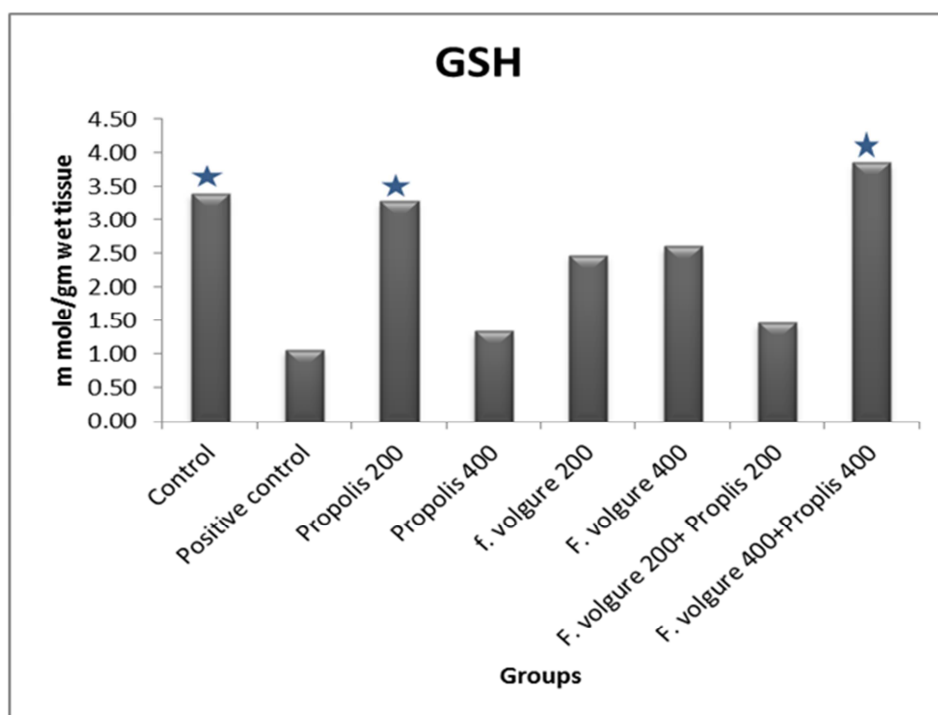


Fig. 7. Shows the mean of GSH concentration in rats subjected to alloxan and treated with Propolis & *F. vulgare* doses for one month.

Catalase shows a significant increase ($p < 0.05$) in C., D.M. +200pro, D.M. +400pro, D.M. +200F.v, D.M. +400F.v, D.M. +200pro + 200F.v, D.M. +400pro + 400F.v. when compared with Positive control (Diabetics) as in table 1 & fig. 6 Where Mean and S.E was (0.61 ± 0.04) in Positive control (Diabetics) and were (1.45 ± 0.07) and (0.95 ± 0.06) in C., and D.M. + 400pro respectively.

4. Discussion

4.1. Fasting Blood Glucose

These studies suggested that the propolis and *Foeniculum vulgare* have beneficial effects on reduction of blood sugar levels in alloxan induced diabetes rats. Regarding to the results of fasting blood glucose, it shows a significant decrease ($p < 0.05$) in C., D.M. +200pro, D.M. +400pro, D.M. +200F.v, D.M. + 400F.v, D.M. + 200pro + 200F.v, D.M. + 400pro + 400F.v. when compared with Positive control (Diabetics) may be due to destroy the insulin-producing β -cells of islets of Langerhans in the pancreas this results agreement with (Hanan and Nareman, 2015); (Sakudelski, 2001); (Bankova, 2009); (Lenzen, 2008); (Altaee, 2014); (Mhaidat, *et al.*, 2015) and (Mostafa, *et al.*, 2015).

4.2. Insulin

Regarding to the results of Insulin, it shows a significant increase ($p < 0.05$) in C., D.M. +200pro, D.M. +400pro, D.M.

+200F.v, D.M. + 400F.v, D.M. + 200pro + 200F.v, D.M. + 400pro + 400F.v. when compared with Positive control (Diabetics) may be due to destroy the insulin-producing β -cells of islets of Langerhans in the pancreas This results agreement with (Al-Hariri *et al.*, 2011) and (El-Missiry *et al.*, 2004).

4.3. Antioxidants

Insufficiency of antioxidant defense system leads to elevation in the levels of free radicals. Elevated level of free radicals may lead to disruption in cellular functions, oxidative damages to membranes and enhanced susceptibility to lipid peroxidation (Amin *et al.*, 2013; Baynes, 1991).

4.3.1. Malondialdehyde (MDA)

Regarding to the results of (MDA), it shows a significant decrease ($p < 0.05$) in C., D.M. +200pro, D.M. +400pro, D.M. +200F.v, D.M. + 400F.v, D.M. + 200pro + 200F.v, D.M. + 400pro + 400F.v. when compared with Positive control (Diabetics) may be due to indicate of oxidative stress and depression of the antioxidant defense system. This results agreement with (Amin *et al.*, 2013); (Oršolic *et al.*, 2012); (Hemieda *et al.*, 2015); (Al-Hariri *et al.*, 2011) and (Orsolic *et al.*, 2013)

4.3.2. Superoxide Dismutase (SOD)

Regarding to the results of (SOD), it shows a significant decrease ($p < 0.05$) in C., D.M. +200pro, D.M. +400pro, D.M.

+200F.v, D.M. + 200pro + 200F.v, D.M. + 400pro + 400F.v. when compared with Positive control (Diabetics) may be due to disruption in cellular functions, oxidative damages to membranes and depression of the antioxidant defense system. This results agreement with (Zhu *et al.*, 2010). On the other hand this results disagreement with (Amin *et al.*, 2013); (Babatunde *et al.*, 2015) and (LIU Yan *et al.*, 2009).

4.3.3. Glutathione-S-transferase (GST)

Regarding to the results of (GST), it Shows a significant increase ($p < 0.05$) in C., and with D.M. + 200 F.v. when compared with Positive control (Diabetics) may be due to increase of free radical in the tissue. This results agreement with (Ramkumar *et al.*, 2009) and (Sridhar *et al.*, 2014).

4.3.4. Hepatic Reduced Glutathione (GSH)

Regarding to the results of (GSH), it Shows a significant increase ($p < 0.05$) in C., D.M. +200pro, D.M. + 400pro + 400F.v. when compared with Positive control (Diabetics) may be due to attributed to the inhibition of its regenerating enzyme glutathione reductase (GSH- R), regression of the antioxidant recycling mechanism in diabetic rats. This results agreement with (Amin *et al.*, 2013); (Ramkumar *et al.*, 2009); (Hemieda *et al.*, 2015); (El-Missiry *et al.*, 2004) and (Sridhar *et al.*, 2014)

4.3.5. Catalase (CAT)

Regarding to the results of (CAT), it shows a significant increase ($p < 0.05$) in C., D.M. +200pro, D.M. +400pro, D.M. +200F.v, D.M. + 400F.v, D.M. + 200pro + 200F.v, D.M. + 400pro + 400F.v. when compared with Positive control (Diabetics) may be due to disruption in cellular functions, oxidative damages to membranes and depression of the antioxidant defense system. This results agreement with (Ramkumar *et al.*, 2009); (Hemieda *et al.*, 2015); (El-Missiry *et al.*, 2004) and (Sridhar *et al.*, 2014).

5. Conclusion

- 1 Propolis includes many anti-oxidants like phenolics and flavonoids. One of the major components of *Foeniculum vulgare* seed's essential oil is trans anethole. *Foeniculum vulgare* (fennel) possesses antioxidant and anti-diabetic activities.
- 2 Propolis and *Foeniculum Vulgare* possesses hypoglycemic activities in addition to its ability to ameliorate oxidative stress that induce organ dysfunction.

Recommendation

We recommend with using Propolis and *Foeniculum Vulgare*

in hypoglycemic and oxidative stressed patients.

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