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Effect of Honey on Hormonal, Enzymatic and Antioxidant Markers of Diabetic Rats

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ABSTRACT

Diabetes mellitus is a disorder in which the body does not produce enough or respond normally to insulin, causing abnormally high levels of blood sugar (glucose). Honey, a natural sweet substance produced by honey bee, can provide beneficial effects on body weight and blood lipids of diabetic patients. This study aims to experimentally induction of alloxan-type 2 diabetes mellitus in rats; and estimation the effect of honey on the hormonal, liver enzymatic and antioxidant markers.A total of 36 adult male albino rats were purchased, acclimated and divided randomly and equally into three groups as following: HG that neither alloxan-injected nor honey received; DG that injected alloxan without receiving honey; and DTG that injected alloxan and received a daily oral dose of honey. After 30 days, rats of all study groups were lightly anesthetized, and subjected to direct collection of whole blood. The obtained sera were used to measurement of insulin hormone and liver enzymes [alkaline phosphatase (ALP), alanine aminotransferase (ALT), and aspartate aminotransferase (AST)], and the activities of antioxidants [catalase, superoxide dismutase (SOD), and glutathione peroxidase (GPx)] by the quantitative ELISA. The findings of insulin hormone were increased significantly in DTG when compared to values of both HG and DG. Regarding liver enzymes, the findings of ALP, ALT and AST of DTG were decreased significantly when compared to values of DG but remain significantly higher than those of HG. Concerning the antioxidants, the findings of catalase, GPx and SOD were increased significantly in DTG when compared to values of DG but still significantly lower than those of HG. This study concluded the ability of honey to ameliorate the levels of insulin hormone, liver enzymes and antioxidants; however, the mechanisms by which the honey exerts its effect on insulin levels and glucose homeostasis in diabetic individuals remain to be fully elucidated. Therefore, additional investigations are required to demonstrating the efficacy and safety of honey as a complementary or alternative therapy for managing diabetes.

1. Introduction

Diabetes mellitus is a chronic metabolic disorder, which characterized by the inability of body to produce or effectively utilize insulin causing an elevated levels of blood glucose and a wide range of health complications, if unmanaged, including cardiovascular diseases, nerve damage, kidney failure, skin and mouth conditions, as well as eye and hearing impairment (Al-Shaeli et al., 2022; Tomic et al., 2022; Antar et al., 2023). The prevalence of diabetes has been steadily increasing worldwide, and the number of adult living with one type of diabetes is now over four times higher than in the past, posing a significant burden on healthcare systems and economic losses (Harding et al., 2024; Parker et al., 2024). Several factors have been identified as contributors to the rise in diabetes prevalence such as sedentary lifestyles, unhealthy dietary habits, and increasing rates of obesity (Alam et al., 2021). Diabetes can be broadly classified into two main types; type 1 that characterized by the autoimmune destruction of pancreatic β-cells leading to insulin deficiency (Eizirik et al., 2023), and type 2 that associated with insulin resistance and impaired insulin secretion (Roden et al., 2024). Therefore, effective management of diabetes requires a multifaceted approach including lifestyle modifications, pharmacological interventions, and regular monitoring of blood glucose levels (Sugandh et al., 2023). Diabetes self-management education and support play a crucial role in empowering individuals with diabetes to navigate their daily self-care and improve clinical outcomes (Olorunfemi et al., 2025). In addition, the development of novel therapies has shown promise in the management of diabetes and its associated complications (Chen et al., 2025).

Honey, the golden elixir produced by industrious honeybees, has captivated the human imagination for millennia, serving not only as a delectable sweetener but also as a versatile ingredient in various culinary and medicinal applications (Kumar et al., 2024; Salama and Chennaoui, 2024). This remarkable natural substance is a complex matrix of sugars, vitamins, minerals, and an array of bioactive compounds that have been the focus of extensive research (Ranneh et al., 2021; Al-Sarray and Al-Shaeli, 2022; Valverde et al., 2022). Studies have shown that honey possesses potent antimicrobial activity against a wide range of pathogenic bacteria, fungi and viruses making it a valuable asset in the field of wound management and infection control (Tashkandi, 2021; Al-Shaeli et al., 2022; Yupanqui Mieles et al., 2022). The benefit activity of honey is attributed to its low pH, high osmolarity and the presence of various phytochemicals such as hydrogen peroxide, phenolic compounds, and methylglyoxal which can disrupt the cell walls and interfere with the metabolic processes of diseases (Saranraj and Sivasakthi, 2018; Brudzynski, 2020). Interestingly, the beneficial properties of honey are not limited to its topical applications since several insights shown that honey having the ability to exhibit systemic effects making it a potential candidate for a treatment of various infectious diseases (Hussain, 2018). The diverse and complex composition of honey is a testament to the remarkable adaptations of the honeybee which has evolved specialized behaviors and partnerships with therapeutic symbionts to facilitate the production of this unique substance (Winston, 2014; Machado et al., 2023). The incorporation of exogenous materials such as proplis and endogenous products such as peptides and royal jelly further enhances the distinctive properties of honey, making it a truly remarkable and multifaceted natural substance (Çelik and Aşgun, 2020; Nowak et al., 2021).
The investigation of honey's therapeutic potential has led to the discovery of its effectiveness against a variety of human diseases (Eteraf-Oskouei and Najafi, 2013; Almasaudi, 2021). Furthermore, the activities of antioxidants and free radical-scavengers of honey have been well-documented highlighting its potential as a natural remedy for various ailments (Faúndez et al., 2023). This study aims initially to experimentally induction the alloxan-type 2 diabetes mellitus in rats; and then, estimation the effect of honey by measurement the concentrations of insulin hormone and liver enzymes (ALP, ALT, and AST), and the activities of antioxidants (CAT, SOD, and GPx).

2. Methodology

Ethical Approval
The current study was licensed by the Scientific Committee of the College of Veterinary Medicine (University of Wasit, Wasit, Iraq).

Preparation of alloxan and honey
Following the manufacture instructions of alloxan monohydrate (Sigma Aldrich, USA), the contents of each vial was dissolved in normal saline at room temperature, and shacked vigorously. Prior to alloxan-injection, the study animals were fasted for at least 12 hours.

Study animals and experimental design
A total of 36 adult male albino rats of 129-168g weight, were purchased, transferred to the Lab Animal House, and acclimated for one week by providing the pellet and tap water with exposure to 12/12 hours of light / dark. Then, the rats were divided randomly and equally into three groups as following:

1. Healthy group (HG): Rats were neither alloxan-injected, nor honey received, and fed normally.
2. Diabetic group (DG): Rats were injected a single dose of alloxan (150mg/Kg/BW) intraperitoneally, but doesn't receive honey, and fed normally.
3. Diabetic-treated group (DTG): Rats were injected a single dose of alloxan (150mg/Kg/BW) intraperitoneally. After ensuring of diabetes, they received a daily oral dose of honey (15ml/Kg/Bw), and fed normally.

Sampling
After the end of experimental study (30 days), rats of all study groups were lightly anesthetized, and subjected to direct collection of whole blood from the heart using a disposable syringe into labeled free-anticoagulant glass-gel tube. Post centrifugation (5000rpm for 5min), the obtained sera were transferred into labeled 1.5ml Eppendorf tubes and kept frozen at -4°C until be used (Razooqi et al., 2022; Al-Khatawi et al., 2025).

Biochemical analysis
According to manufacturer instructions of the quantitative ELISA Kits (SunLong Biotech, China), the solutions of each kit in addition to sera were prepared, processed, and the optical density was read at an absorbance of 450nm using the Automated Microplate Reader (Agilent Technologies, USA). Then, the ODs and concentrations of the Standards in addition to the ODs of samples were plotted on the log scale to calculate the concentrations of samples.

Statistical analysis
The One-Way ANOVA in GraphPad Prism Software was applied to detect significant differences between values (mean ± standard error) of the study groups at $p<0.05$ (Gharban, 2022)..

3. Results
Significantly, the findings of insulin hormone were increased ($p<0.0001$) in DTG (7.569 ± 0.34) when compared to the values of both HG (4.063 ± 0.241) and DG (1.901 ± 0.079), (Figure 1). In liver enzymes, significant differences ($p<0.05$) were showed in values of study groups. Regarding ALP enzyme, the findings of DTG (6.833 ± 0.528) were decreased significantly ($p<0.01$) when compared to values of DG (10.325 ± 0.34) but remain significantly ($p<0.01$) higher than those of HG (2.717 ± 0.317), (Figure 2). Concerning the ALT enzyme, the findings of DTG (417.075 ± 32.57) were reduced significantly ($p<0.01$) in comparison with the values of DG (870.175 ± 53.154) but remains significantly ($p<0.0001$) higher than values of HG (182.1 ± 16.37), (Figure 3). Relation to AST enzyme, the findings of DTG (1.604 ± 0.107) were significantly ($p<0.0001$) lower than values of DG (2.583 ± 0.111) but higher than those of HG (0.55 ± 0.077), (Figure 4).

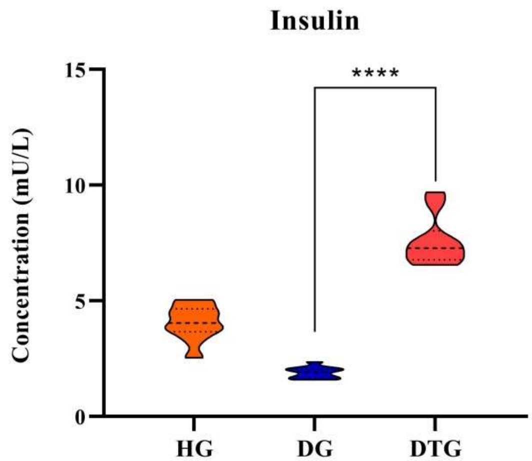

Figure 1. Concentration of insulin hormone among the three study groups.

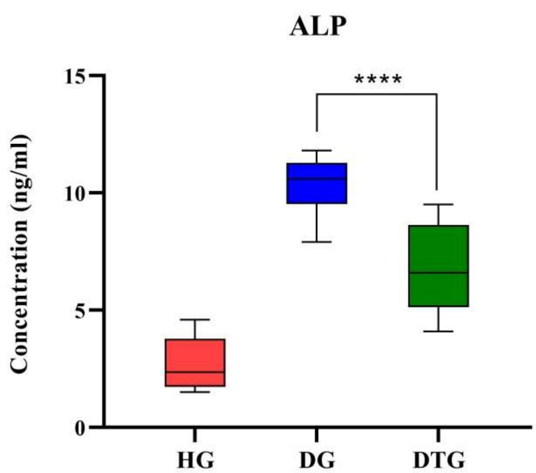

Figure 2. Concentration of ALP enzyme among the three study groups.

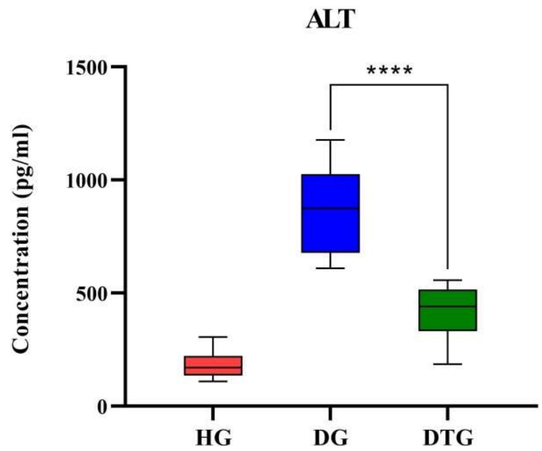

Figure 3. Concentration of ALT enzyme among the three study groups.

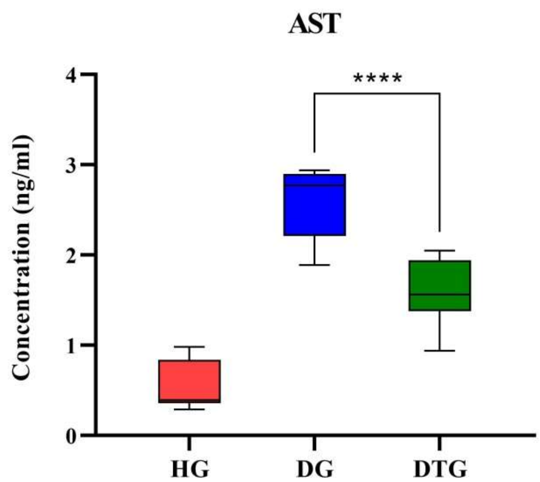

Figure 4. Concentration of AST enzyme among the three study groups.

Among the antioxidants, the findings of catalase were increased significantly ($p<0.009$) in DTG (22.85 ± 0.842) when compared to those of DG (11.417 ± 1.356) but still significantly ($p<0.0001$) lower than the values of HG (31.375 ± 0.766), (Figure 5). For GPx enzyme, the findings of DTG (52.45 ± 3.358) were significantly ($p<0.001$) higher than the values of DG (23.567 ± 2.384) but lower than those of HG (93.075 ± 4.986), (Figure 6). Concerning the findings of SOD enzyme, significant elevation ($p<0.0001$) in values of DTG (7.518 ± 0.373) was seen when compared to those of DG (4.058 ± 0.315) but remain lower than those of HG (12.569 ± 0.306), (Figure 7).

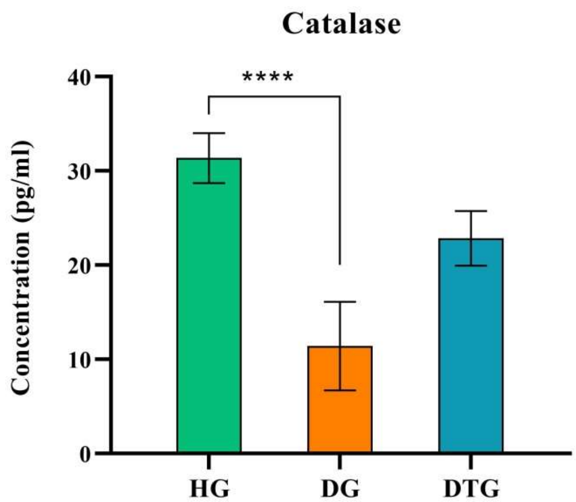

Figure 5. Concentration of catalase among the three study groups.

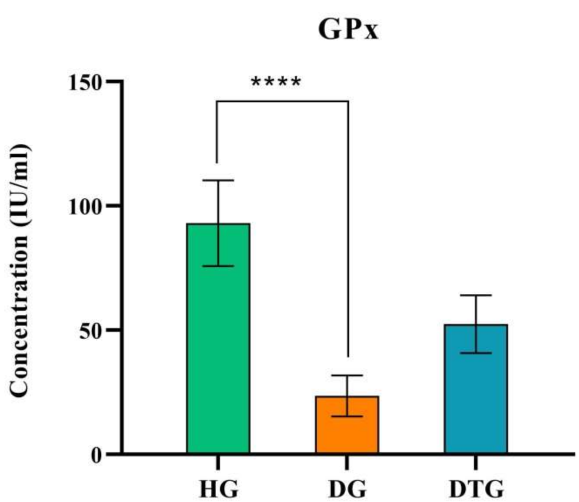

Figure 6. Concentration of GPx among the three study groups.

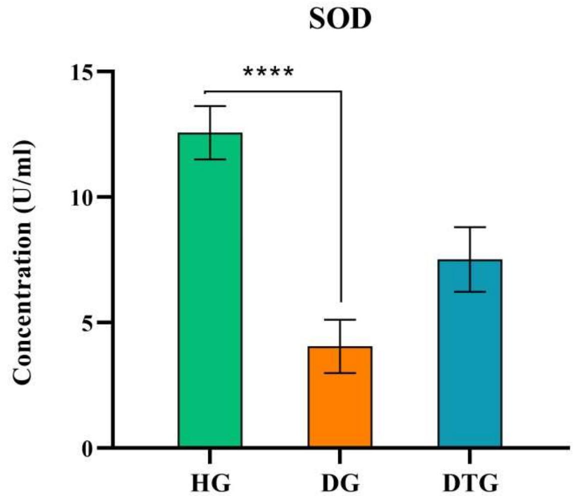

Figure 7. Concentration of SOD among the three study groups.

3. Discussion

In current study, the findings showed that honey administration increases the levels of insulin more than the values of both diabetic and healthy rats. Worldwide, accumulative evidence indicates that the bioactive compounds found in honey play a crucial role in regulating glucose and insulin sensitivity (Cianciosi et al., 2018; Pasupuleti et al., 2020; Chen et al., 2022). In one study, the findings shown that certain flavonoids such as galangin and pinocembrin can ameliorate insulin resistance in liver cells, suggesting a potential mechanism for the anti-diabetic effects of honey (Ali et al., 2020; Taleuzzaman et al., 2020). Further, honey has been observed to possess hypoglycemic properties, potentially due to its ability to stimulate insulin secretion and enhance glucose uptake by peripheral tissues (Sirisha et al., 2021; Chen et al., 2022). Although, a meta-analysis study of 18 small studies found that some types of honey slightly lowered participants' fasting blood sugar, a systemic review of clinical trials reported that getting too much honey actually can increase the glucose levels of people with type 2 diabetes (Zamanian and Azizi-Soleiman, 2020; Ahmed et al., 2023). Another small Turkish study recorded that the daily administration of 5-25g of honey to type 2 diabetic patients for four months reduced their HbA1c; and the higher daily amounts of honey were increasing the level of HbA1c (Akhbari et al., 2021).

Our results reported the beneficial role of honey in reducing the concentration of liver enzymes. The liver is a central organ in the body's homeostasis which responsible on various metabolic processes and is vulnerable to exposure for toxins, bacteria, and antigens derived from food (Kubes and Jenne, 2018; Albillos et al., 2020). Loss of insulin effect in liver tissues can lead to glycogenolysis, increase in hepatic glucose production, and abnormalities in triglyceride storage and lipolysis in insulin-sensitive tissues (Sharabi et al., 2015). This causes an excess in free fatty acids that directly toxic to hepatocytes and increase the proinflammatory cytokines which contribute to hepatocellular injury (Byrne, 2010; Mohamed et al., 2016). Bonnet et al. (2011) show that an elevation in either ALP or ALT is associated with increased systemic and liver insulin resistance in both men and women, and hypothesized that elevation in these enzymes is suppressed by insulin. In a previous study, Vozarova et al. (2002) determined that hepatic enzyme elevations is linked to the development of type 2 diabetes and the percent body fat; while elevated ALT was associated with an increase in hepatic glucose output. In type 2 diabetes and liver diseases, alteration in hepatic glucose metabolism such as increased post-absorptive glucose production and diminished glucose uptake following carbohydrate ingestion can occur indicating insulin resistance as central pathological principles (TC, 2005; Raddatz and Ramadori, 2007; Solis-Herrera et al., 2021). Recent research has suggested that honey may have a positive effect on liver enzymes, which are markers of liver health and function (Agbatutu et al., 2022; Sekar et al., 2023; Garmroodi et al., 2024). Several studies reported that these effect were applied on lipid profile, glycemia, and hepatic antioxidant status suggesting that it may help to alleviate liver damage and improve overall liver function (Boshra et al., 2024; Hamamah et al., 2024; Rezaei et al., 2024). Honey's potential to enhance insulin secretion, reduce apoptosis and promote proliferation of pancreatic β-cells as well as its ability to regulate glucose metabolism in hepatocytes, and contributing to its beneficial effects on liver enzymes (El-Aarag et al., 2024; Song et al., 2024; Srinivasan et al., 2024; Jagua-Gualdrón et al., 2025).

This study indicates that administration of honey to diabetic rats resulted in increasing the levels of antioxidants suggested the high free-radical scavenging activity of honey. Oxidative stress, defined as an imbalance between the production of reactive oxygen species and the ability of the body to neutralize them through antioxidant defenses (Demirci-Cekic et al., 2022). This imbalance could be exacerbated with diabetes, as hyperglycemia causes the overproduction of free radicals, in addition to auto-oxidation of glucose, activation of polyol pathway and the formation of advanced glycation end-products (Ighodaro, 2018;

Yaribeygi et al., 2019; Yamaguchi et al., 2024). A previous study demonstrates the role of honey in preventing of hepatic damage induced by obstruction of common bile duct due to increasing the activity of nitric oxide in the liver tissue by elimination of toxic free radicals by the nitric oxide existed largely in honey (Erguder et al., 2008). Recently, numerous studies have demonstrated that interventions aimed at reducing oxidative stress, such as the use of antioxidant supplements, can improve insulin sensitivity and glycemic control as well as potentially preventing or delaying the onset of diabetic complications (Fong et al., 2022; Shrivastav et al., 2023). The antioxidant capacity of honey is largely attributed to its rich content of phenolic compounds, which are secondary metabolites produced by plants (Wilczyńska and Żak, 2024). These compounds, as taxifolin and syringaldehyde, have been observed to possess potent antioxidant properties, helping to neutralize harmful free radicals and protect cells from oxidative stress (Carina Biluca et al., 2021; Laaroussi et al., 2021). However, the diverse range of honey types, each with its unique physicochemical properties and bioactive compounds, suggests that the activity of honey on antioxidant levels may vary depending on the specific type and source (Pătruică et al., 2022; Al-Kafaween et al., 2023).

4. Conclusion

This study insight the ability of honey to ameliorate the levels of insulin hormone, liver enzymes and antioxidants; however, the mechanisms by which the honey exerts its effect on insulin levels and glucose homeostasis in diabetic individuals remain to be fully elucidated. Therefore, additional investigations are required to demonstrating the efficacy and safety of honey as a complementary or alternative therapy for managing diabetes.

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