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Study for Evaluation of the Protective Effects of Urtica Dioica Leaves on Cardiac Function In Alloxan-Induced Diabetic Albino Rat

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URTICA DIOICA (UD) is used for a number of therapeutic purposes. Has traditionally been used in the control of cardiovascular disorders, especially hypertension. Also, the leaf extract of UD has been reported to improve glucose homeostasis *in vivo*. This raises the question of the relationship between UD, diabetes, and heart disorders. Therefore, this study aimed to evaluate the effect of watery leaf extract UD on the heart parameters associated with diabetes mellitus (DM) in Wistar rats. Animals were divided into 4 groups (N = 25). The untreated normal control rats only received distilled water (n = 8).), The diabetic control rats group received alloxan 120 mg/Kg body weight (n = 7), the diabetic rat group treated with UD at 250 mg/kg body weight (n = 5), and the diabetic rats that received UD extract at 500 mg/Kg body weight (n = 5) orally twice daily for 5-6 days. Data showed that in the diabetic group heart rate decreased and induced bradyarrhythmia. After treating diabetic rats with 250 mg/kg enhancement in heart rate was recorded. Additionally, increasing the UD concentration to 500mg/kg further increases the heart rate to the normal value. The current study indicates a widening in QRS, which seems to be disturbances of intraventricular conduction that can be seen in right and left bundle branch blocks, heart failure, and myocardial ischemia. Conclusively, these data show that UD appears to have antidiabetic and noncytotoxic properties, it is associated with reducing the effect of diabetics on the heart.

Keywords: *Antihypertension; Anti-arrhythmia; Anti-diabetes; Glucose; Urtica dioica.*

Introduction

Along with cardiovascular diseases and cancers, type 2 diabetes mellitus (DM2) has a big impact on society and well-being. Oftentimes, this illness causes death and impairment. It is one of the top five leading causes of death worldwide [1]. Diabetes mellitus is a group of metabolic disorders caused by hyperglycemia and glucose intolerance. It is generally accepted that there are two forms of diabetes mellitus. Type-1 diabetes is characterized. By insufficient insulin production by pancreatic cells and type-2 diabetes is characterized by the development of the body's insulin resistance [2]. More than 90% of people with diabetes have type 2 diabetes [3].

Clinically, type 2 diabetes patients with cardiovascular disease have a wide range of symptoms, including heart failure, silent ischemia, intermittent claudication, stroke, myocardial infarction, arrhythmia, and sudden death sudden death [4]. This clinical variance is caused by several variables, including microvascular dysfunction, arterial stiffness, and atherothrombosis associated with diabetes[5]. Prediabetes already shows many of the abnormalities linked to type 2 diabetes [6]. Also linked to prediabetes is an increased risk of cardiovascular disease. In addition to the

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classification of the glucose metabolism status, ongoing measures of hyperglycemia have been linked to cardiovascular disease [6- 8].

It is possible to evaluate the cardiac autonomic function without using any intrusive procedures by calculating heart rate variability (HRV), which symbolizes the interplay of the parasympathetic and sympathetic components of the autonomic nervous system on the sinus node. Low HRV, a recognized sign of cardiovascular autonomic dysfunction, is associated with an increased risk of sudden heart attacks and ventricular arrhythmias [9].

Natural products, whether plant extracts or pure substances propose countless choices for additional therapeutic supplies because of the incomparable accessibility of chemical diversity. Historically, humans have depended upon medical plants to treat patients[10]. Although therapeutic research has made tremendous strides, there is still a desire for potent and effective analgesics. So, it has been amply established that a variety of plant-derived substances play a significant role in the process of finding new techniques to cure diseases' symptoms [10]. One of the most important nowadays medicinal plants is known as Stinging Nettle [11]. This plant belongs to the *Urtica dioica* species [12] and in Arabic known as Qaras.

Testai and his colleagues (2002) examined how nettle root extracts affected the cardiovascular system. This study was conducted on the aortas with or without endothelium. Only, in aortas with endothelium, vasodilatory activity has been seen. These results demonstrate the ability of the stinging nettle to induce hypotensive responses via vasodilatory effects, as a result of detrimental inotropic action, potassium channel opening, and endothelial nitrogen oxide production [13]. Nettle did not alter the blood pressure of mice, however, cats experienced bradycardia and a strong hypotensive reaction [14]. El Haouari *et al.* (2006) claim that flavonoids are responsible for the antiplatelet effect of *Urtica dioica*. These results validate the earlier usage of Urtica dioica in the prevention and treatment of cardiovascular diseases [15].

Material and Methods

Plant Material

According to the technique described by Verma *et al*. in 2009 fresh and mature leaves of Urtica dioica were collected from the field in Zakho, Iraq. After being shade-dried, the leaves were manually combined into smaller sizes, kept refrigerated, and protected from light throughout the extraction procedures. The 500 mL of 99 percent ethanol was used to create the 120 grams of powdered *Urtica dioica* leaves after properly combining them and allowing them to stand with the bowel covered for 48 hours [16]. To extract the leaves using cold solvent extraction, a 25 L acidified aqueous-methanol solution with 50% methanol and 1% acetic acid was homogenized with the leaves. Filtration was used to get rid of the extract's residue after evaporation at 40°C. A 3.5 pH adjustment was then made to the aqueous portion. After evaporating the extract and fractions at room temperature, they were then dried in the air. Before investigation and subsequent use, fully dried fractions and extract were weighed and kept at a temperature of -20°C in sealed containers.

Experimental Animal

Male healthy adult albino rats weighing between 250–300 grams were used in this study. In the animal house of Zakho University, rats were grown and housed in plastic cages with bedding made of wooden pellets in a room with a constant temperature of 25 ^{o}C. The animals were kept in a 12/12-hour cycle of light and darkness during the whole study. The rats were provided with clean tap water and a regular rat diet (a mixture of protein, fat, and carbohydrate). The University of Zakho Animal Research Ethics Committee approved rats' research methods, following the standards outlined in the National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals.

Preparing Diabetic Animals

Alloxan Monohydrate (Sigma), dissolved in sterilized Phosphate-Buffered Saline (PBS), was injected intraperitoneally into rats that had been overnight fasted in order to cause type 2 diabetes mellitus. Prior to administering Alloxan, the rats' baseline blood glucose levels were measured manually by glucometer. Diagnosis of diabetes was made after 72 hours of alloxan administration by assessing the fasting rats' blood glucose levels, those rats with fasting blood sugar levels greater than 220 mg/dL were accepted as diabetic [17].

Treating Diabetic Animals with Urtica dioica

Twenty-five rats were divided into four main groups The first group, the normal untreated control group, was simply treated with distilled water (n = 8), The second group, the diabetic control group, was simply treated with 200 mg / Kg body weight Alloxan (n = 7), The third group, was the diabetic group treated with *Urtica dioica* at dose 250 mg/ kg body weight (n = 5), and the fourth group, was the diabetic group treated with *Urtica dioica* dose at 500 mg / Kg body weight (n = 5), for five to six days, orally twice daily. The animals were then given an overnight fast before

blood was collected to estimate their fasting blood glucose levels.

Preparation of Animals

By giving 80 mg ketamine/kg of body weight and 13 mg xylazine/kg intravenously, all animals were anesthetized. A 24-gauge catheter is used to give drugs directly into the tail vein of rats. Rat limbs were then fixed with sewing pins on a waxy dissection tray and ECG needle electrodes from AD Instruments, Sydney, Australia, were positioned on the left hind legs and forelimbs of the experimental subjects. Subsequently, these ECG signals underwent amplification using AD Instruments' Power Lab and Bio Amplifiers. The digitized ECG data was then analysed through Labchart7 software from the same manufacturer.

Statistical Analysis

The median and interquartile range for each result is presented together. The Kruskal-Wallis test was used to compare all non-parametric variables, and the results were then adjusted using Dunn's test. Group averages were compared using one-way ANOVA, and any differences were determined using the Tukey post hoc test. P-value 0.05 was chosen to denote statistically significant for all two-tailed test data. For reporting resting heart rate, beats per minute are utilized. Sudden bradycardias were determined and identified when the heart rate dropped suddenly by at least 30 beats per minute. Heart rate (Hz) time (s) drop is denoted as "beats lost". We also calculated total bradycardia, which is the sum of bradycardia frequency and amplitude (beats lost/min). To calculate QT, Bazett's approach, which converted the QT interval to HR, is a very useful tool. This depends on multiplying the QT interval by the square root of the RR interval. GraphPad Prism 7 software (San Diego, California, USA) was used to analyze the data.

Results

Effects of Diabetes Mellitus Caused by Alloxan

Heart rate (HR) is the total number of heartbeats in a certain amount of time, usually one minute (beats per minute, bpm). Wistar rats' hearts beat between 242 and 336 beats per minute while they were sedated with xylazine and ketamine (Miranda *et al*. 2007). According to this investigation, diabetic rats' HR fell non-significantly from 276 ±10.98 to 258.6 ±9.532 when compared to the control group, and this impact led to bradyarrhythmia. The period between successive R wave peaks, or the RR interval, rose from 0.2174 ±0.010 to 0.2323 ±0.0101 in diabetic rats as compared to the matching control group. Similar to this, incensement in the JT Interval(s), QTc Interval (s), QT Interval (s), QRS Interval (s), and PR Interval (s), was seen in diabetic rats. As demonstrated, the alloxan-induced diabetic rats' QTc value increased from 0.104 ±0.008 to 0.122 ±0.013. (Figure 1C). However, compared to the control, P Amplitude (V), P Duration (s), and ST Height (μV) all reduced non-significantly.

Effect Of Urtica dioica on The ECG Of Diabetic Rat

Urtica dioica's effects on RR, HR, QTc, QRS, and QT at dosages of 250 and 500 mg / kg are demonstrated in Table 1 and Figure 1. Comparing the HR of the Urtica Dioica treated group to that of the control group and the diabetes group 276 ±10.98 and 258.6 ±9.532, respectively shows a further drop to 246.7 ±21.73. This impact intensifies bradyarrhythmia even further. Following ECG recording for 15 minutes, injection of *Urtica dioica* extracts at a dose of 500 mg / kg indicated a non-significantly ($P>0.05$) elevated HR to 299.8 ±15.72, thus reducing the impact of bradyarrhythmia on the heart. Compared to the diabetic rats and the control group, the RR interval increased non-significantly in the group treated with 250 mg/kg of Urtica dioica extract.

Between Q and S waves is the QRS complex. Its length displays the period at which depolarization spread across the ventricles. Critical information on the heart's electrical activity is provided by analyzing the duration of QRS complexes. While broad QRS complexes represent intraventricular conduction and ventricular rhythms abnormalities that can be found in myocardial ischemia, heart failure, and left and right bundle branch blockages, narrow QRS complexes are observed in supraventricular arrhythmias. In this study, broad QRS observed in diabetics compared to the control group. However, compared to other groups, the group that received *Urtica dioica* at a dose of 500 mg/ kg body weight appeared to have a narrow QRS complex (0.01494 ± 0.0005 control, 0.01775 ± 0.0020 diabetic rats, 0.01734 ± 0.0002 250mg/kg *Urtica dioica* and 0.01292 ± 0.0025 at 500mg/kg of *Urtica dioica*). In this work, the diabetic group has a longer QT interval and QTc. Furthermore, extension tended to show in the 250mg / kg group as compared to the 500mg / kg *Urtica dioica* treated group.

Several cardiac arrhythmias, involving the most widespread one, known as atrial fibrillation, demonstrate the absence or modification of the P wave. The PR interval in the control group to the diabetic group ranges from 0.048 ± 0.0012 to 0.052 ± 0.0018 and its length appears to be non-significantly

affected by *Urtica dioica* at doses of 250mg/ per kg and 500 mg / kg, 0.0476 ± 0.0027 and 0.0446 ± 0.0011, correspondingly. In this study, the P wave in the 250 mg / kg-treated group of rats increased to 0.016 ±0.00 when compared to the diabetic group. However, the P wave duration was reduced non significantly in the group treated with 500 mg/ kg. Subsequently, minor elongation, *Urtica dioica* high concentration (500mg/ per kg) returned the p wave to a virtually normal control value.

Discussion

The heart's electrical activity is reflected in electrocardiography (ECG) recordings, which may offer crucial information about the myocardium's structure and function[18,19]. In numerous textbooks and academic papers, the normal and pathophysiological conditions of ECG recordings were extensively discussed . The phytochemical components in the selected plants are recognized as bioactive substances that carry out a variety of functions, including antioxidants, anticancer, antifungal, and antimicrobial activities [18,19]. The hyperlipidemia found in diabetic rats that received alloxan, research suggests that once alloxan is given to control animals, it causes hyperlipidemia [20].

The diabetic-provoked animals in our work displayed a notable loss of weight (data not shown). Because elevated lipid levels increase the risk of cardiovascular infections and are typically present in patients with improperly controlled diabetes, the lipid profile is a vital component that must be retained [22].

Despite the fact that a patient does not pass away from Diabetes but it can cause secondary problems for the patients for instance erectile dysfunction, blindness, and kidney, liver, and heart complications [23]. In the current study, diabetic rats that had been induced by alloxan had a lower heart rate than the control group. These results are consistent with earlier findings as the changes in heart rate were also reduced in streptozotocin-induced diabetic rats [24]. The primary source of diabetes is the oxidative stress brought on via reactive oxygen species (ROS), which results in cell dysfunction, insulin resistance, and finally poor blood glucose tolerance . When fatty acids and glucose are overloaded as a result of a sedentary lifestyle and overeating, reactive oxygen species (ROS) are created [25]. The controversial information available proposing variations provoked by diabetes might be related to variations in analytical and experimental methods. The period following the induction of diabetes, the animal's age, the type of diabetogenic used, and the administration of insulin all had the potential to alter the level of diabetes that was attained and alter the course of various experimental diabetes complications [26]

Numerous hypoglycemic and antidiabetic drugs, including biguanides and sulfonylureas, have been presented for the treatment of diabetes. But even so, these treatment options don't provide long-term blood glucose level control. These drugs are uncommonly used as prolonged use causes cytotoxicity and unwanted side effects for instance liver damage, gastrointestinal discomfort, pancreatic degeneration, and hypoglycemia [27]. Having stinging hairs, the stinging nettle Urtica dioica is an important herbaceous perennial flowering plant. Stinging nettle leaf extract was among the medicinal herbs for which the results of experiments, clinical studies, and clinical trials have all been applicable. It is a famous plant whose roots stems and leaves have been used throughout history. Traditional uses of *Urtica dioica* include the management of cardiovascular diseases, particularly hypertension. In *vivo* improvement of glucose homeostasis by *Urtica dioica* leaf extract has been documented. Some of the effects of hyperplasia prostate may be avoided by consuming *Urtica dioica* root. While extracts from the leaves of the *Urtica dioica* plant are utilized as an anti-inflammatory treatment for rheumatoid arthritis. When used in various concentrations, *Urtica dioica* causes various effects in alloxan-provoked diabetic animals. While the heart rate increased to be higher than the control group at 500mg/kg, it decreased at 250mg/kg. This outcome was consistent with studies that examined the hypotensive effects of various concentrations of an aqueous extract of *Urtica dioica* leaves in rats and demonstrated an acute hypotensive action of *Urtica dioica* that described a direct consequence on the cardiovascular system. The hypotensive effect of *Urtica dioica* leaves was, however, reversible after an hour with the low concentration, while it persisted with the high concentration, indicating a potential toxic effect [28,29]. Similarly, to this, Legssyer et al. (2002) demonstrate that Urtica dioi *Urtica dioica* ca causes significant bradycardia, however, this effect was independent of the effect of cholinergic-1 adrenergic receptors [30]. According to the findings of Qayyum et al. (2016), *Urtica dioica*'s fractions and crude methanolic extract have an antihypertensive potential [31]. This antihypertensive effect of *Urtica dioica* is explained by the effects of calcium channel blockade and Nitric oxide (NO) induced vasorelaxation, and this provides all the necessary information needed for *Urtica dioica* to be used as a medication in the treatment of hypertension [32].

Urtica dioica extract slightly inhibits the enzyme 5-lipoxygenase and hinders leukotriene B4 biosynthesis in a manner dependent on concentration. The extract

exhibited inhibition, which was heavily affected by the amount of prostaglandin biosynthesis [33,34].

Myocardial infarction and hypokalemia have both been linked to prolonged QT intervals in rats [35]. Additionally, just like other ECG parameters, the type of anesthesia appears to have an impact on QT length. QT length was reported in studies to be between 69 and 71 milliseconds in conscious Wistar rats while it is between 75 and 95 milliseconds in rats under xylazine and ketamine anesthesia [36]. Referring to the formula of Bazzet, QTc in Wistar rats was described to be between 133 and 173 milliseconds (ms) during ether anesthesia and between 15 and 56 milliseconds (ms) during conscious telemetry recordings [37].

Other circumstances that can affect the ST segment include intraventricular remedy blocks, Brugada syndrome, and electrolytes and water imbalance. Important changes in the ST segment during myocardial infarction have been seen in rat studies [38] and ischemia of the myocardia [37]. But there are no established, precise standards for what constitutes a significant change in the ST segment. Some scientists assessed the length of ST in rats. The ST segment lasted between 12.3 and 18.1 milliseconds in SD rats under light ether anesthesia [39]. While it was 9.58–14.8 milliseconds in Wistar rats under ether anesthesia. However, the length of The ST segment has little significance when analyzing an ECG. First, because the T wave frequently rises in continuity with the S wave in rat ECG, it is challenging to identify the ST segment. Second, the extension of the ST segment results in an increase in QT (RT) intervals. The two latter parameters can therefore be analyzed more quickly than the ST segment. Consequently, since it is more convenient, the two latter parameters should be examined instead of the ST segment [37].

Conclusion

We draw the conclusion that *Urtica dioica* treatment improved heart function in rats with short-term diabetes mellitus caused by alloxan. This finding indicates that *Urtica dioica* treatment and the more effective dosage stopped or reversed the time-dependent changes in HR, RR, and PR variability.

Acknowledgment

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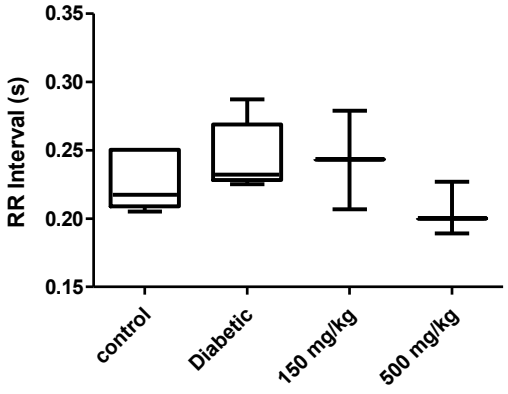
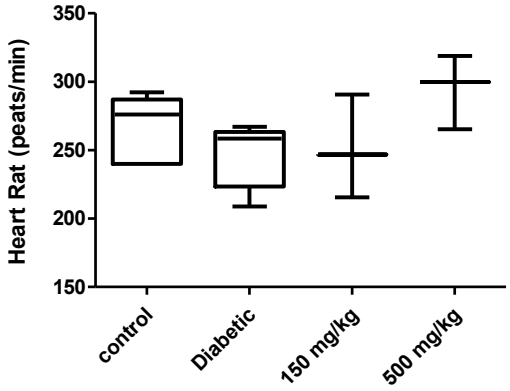
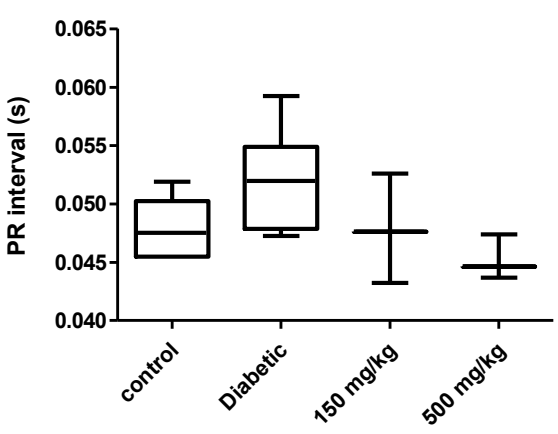
Conflicts of interest

The authors declare no conflict of interest



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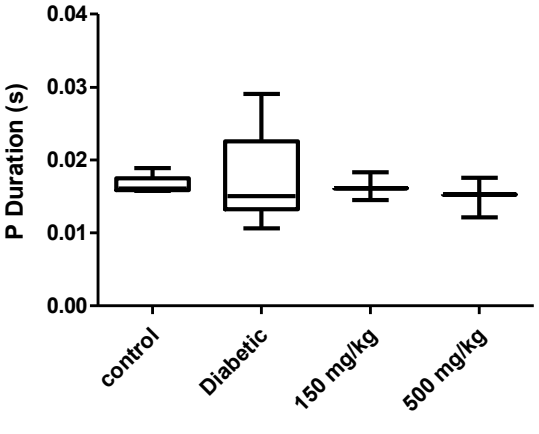
500 mg/kg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control
Diabetic
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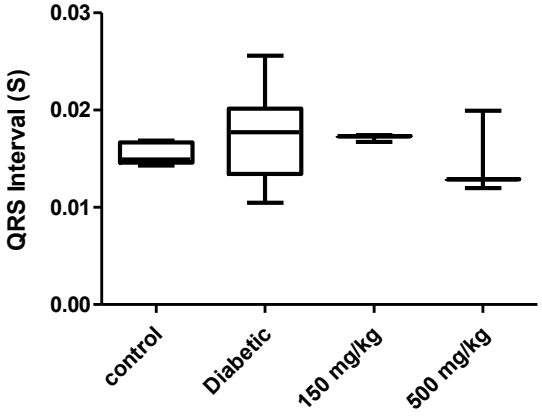
500 mg/kg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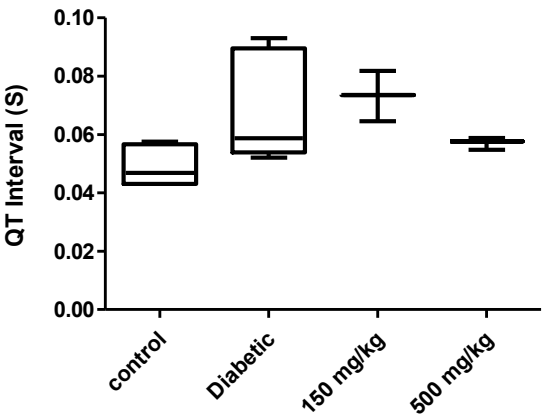
500 mg/kg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Diabetic
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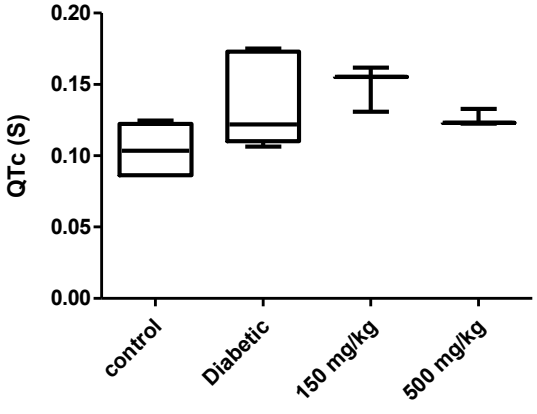
500 mg/kg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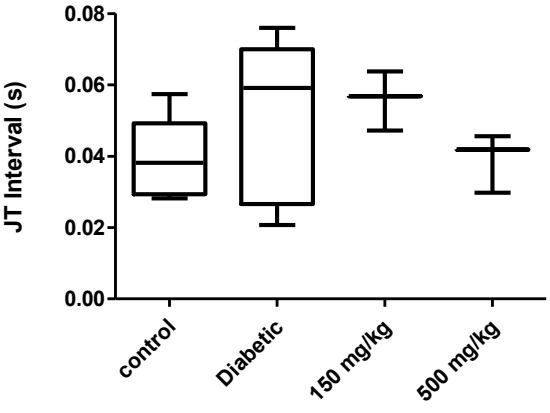
500 mg/kg


JT Interval (s)
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Diabetic
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500 mg/kg

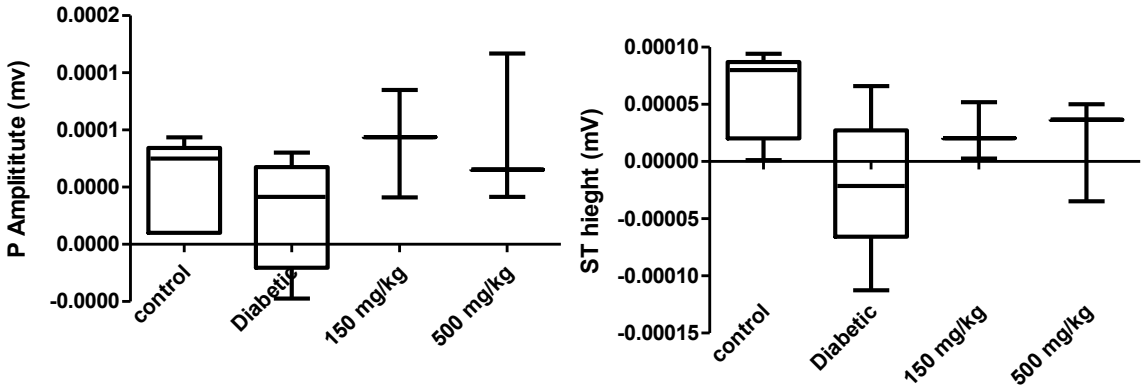

Fig. 1. Reveals the effects of Urticia Dioica (150 and 250 mg/kg BW) on RR intervals (a); Heart rates (b); PR intervals (c); P duration (d); QRS (e); QT intervals (f); QTc (g); JT (h); P amplitude (i) and ST height in diabetic male albino rats.

TABLE 1. The effects of 250 and 500mg/kg/day of Urtica dioica infusion on some heart parameters (Median±interquartile range) in cardiac arrhythmia in diabetics' male albino rats.

Parameter	Control	Diabetics	UD 250mg/kg/day	UD 500mg/kg/day	P-value
HR (BPM)	276 ± 10.98	258.6 ± 9.532	246.7 ± 21.73	299.8 ± 15.72	0.1291
RR Interval (s)	0.2174 ± 0.010	0.2323 ± 0.0101	0.2434 ± 0.021	0.2002 ± 0.011	0.1844
PR Interval (s)	0.048 ± 0.0012	0.052 ± 0.0018	0.0476 ± 0.0027	0.0446 ± 0.0011	0.0915
QRS Interval (s)	0.01494 ± 0.0005	0.01775 ± 0.0020	0.01734 ± 0.0002	0.01292 ± 0.0025	0.7132
QT Interval (s)	0.047 ± 0.003	0.059 ± 0.007	0.074 ± 0.005	0.058 ± 0.001	0.0630
QTc Interval (s)	0.104 ± 0.008	0.122 ± 0.013	0.155 ± 0.009	0.123 ± 0.003	0.0737
P Duration (s)	0.016 ± 0.001	0.015 ± 0.003	0.016 ± 0.001	0.015 ± 0.002	0.8896
P Amplitude(µV)	7E-05 ± 2E-05	4E-05 ± 2E-05	9E-05 ± 3E-05	7E-05 ± 4E-05	0.2257
JT interval (s)	0.038 ± 0.004	0.059 ± 0.007	0.057 ± 0.005	0.042 ± 0.005	0.3322
ST Height (µV)	0.00008 ± 0.00002	-0.00002 ± 0.00003	0.00002 ± 0.00001	0.00004 ± 0.00003	0.1073

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دراسة لتقييم التأثيرات الوقائية لأوراق Urtica Dioica على وظيفة القلب في الجرذان البيضاء المصابة بداء السكري المستحث بالألوكسان

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يستخدم Urtica dioica (UD) لعدد من الأغراض العلاجية. يستخدم تقليديا في السيطرة على اضطرابات القلب والأوعية الدموية ، وخاصة ارتفاع ضغط الدم. أيضًا ، تم الإبلاغ عن مستخلص أوراق UD لتحسين توازن الجلوكوز في الجسم الحي. هذا يثير السؤال عن العلاقة بين UD والسكري واضطرابات القلب. لذلك هدفت هذه الدراسة إلى تقييم تأثير مستخلص الأوراق المائي UD على معاملات القلب المرتبطة بداء السكري (DM) في فئران ويستار. تم تجميع الحيوانات في ٤ مجموعات (العدد = ٢٥). تلقت الجرذان العادية غير المعالجة الماء المقطر فقط (ن = ٨).) ، تلقت مجموعة الجرذان المصابة بمرض السكري الألوكسان ١٢٠ مجم / كجم من وزن الجسم (ن = ٧) ، مجموعة الجرذان المصابة بداء السكري التي عولجت بـ UD عند ٢٥٠ مجم / كجم من وزن الجسم (ن = ٥) ، والجرذان المصابة بداء السكري التي تلقت مستخلص UD بوزن ٥٠٠ مجم / كجم من وزن الجسم (ن = ٥) مرتين يوميًا لمدة ٥-٦ أيام. أظهرت البيانات أن معدل ضربات القلب في المجموعة المصابة بداء السكري ينخفض ويؤدي إلى عدم انتظام ضربات القلب. بعد علاج الجرذان المصابة بداء السكري تم تسجيل زيادة في معدل ضربات القلب بمقدار ٢٥٠ ملجم / كجم. بالإضافة إلى ذلك ، فإن زيادة تركيز UD إلى ٥٠٠ مجم / كجم يزيد من معدل ضربات القلب إلى القيمة الطبيعية. تشير الدراسة الحالية إلى اتساع في QRS ، والذي يبدو أنه اضطرابات في التوصيل داخل البطيني يمكن رؤيته في كتل الفروع اليمنى واليسرى ، وفشل القلب ، ونقص تروية عضلة القلب. أظهر تغيير الوقت المتناقص في فترة QRS عند ٥٠٠ مجم / كجم. لوحظت فروق ذات دلالة إحصائية في فترات QT و QTc. بشكل قاطع ، تظهر هذه البيانات أن UD يبدو أن لها خصائص مضادة لمرض السكر وغير سامة للخلايا ، فهي مرتبطة بتقليل تأثير مرضى السكر على القلب.

الكلمات الدالة: ارتفاع ضغط الدم، مكافحة عدم انتظام ضربات القلب، مكافحة مرض السكري، الجلوكوز والتوازن.