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Therapeutic Effect of Aqueous Extract of *Cocos nucifera* in Streptozotocin-Doxorubicin Induced Rat Model of Diabetic Cardiomyopathy

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ABSTRACT

Objective: Diabetes is the most common endocrine disorders and poses a serious challenge to healthcare worldwide. The pre-valence of diabetes varies in different parts of the world. During diabetes, metabolic remodeling precedes the cardiomyopathy, these changes may contribute to cardiac function. In the present study the effects of *Cocos nucifera* flower extract on cardiac dysfunction during diabetes were investigated. **Methods:** The aqueous flower extract of *Cocos nucifera* was administered for 30 days to the control and experimental rats. After the experimental period animals were sacrificed and the blood samples were used for the analysis of blood glucose, urea, creatinine, marker enzymes, lipid profiles and the histopathological analysis was also done for pancreatic tissue. **Results:** The results showed that the induction of diabetic cardiomyopathy with streptozotocin and doxorubicin increased the glucose level, cardiac marker enzyme activity and the lipid levels. Administration of aqueous extract of Cocos nucifera to experimental rats reduced the glucose and lipid levels and restored the enzyme activity to the normal level. The histopathological analysis showed the restoration by flower extract of pancreas ultra structure impaired by streptozotocin-doxorubicin. The athrogenic and coronary risk indices were significantly increased in doxorubicin-treated and streptozotocin-doxorubicin treated diabetic groups and this was reduced in Cocos *nucifera* treated as well as in aspirin treated group rats ($p<0.05$). We conclude that feeding of the Cocos *nucifera* extract to rats with diabetic cardiomyopathy protect the heart tissue from the complication of diabetes.

Keywords: *Cocos nucifera,* Streptozotocin, Doxorubicin, Diabetes Mellitus, Lipid Profile, Diabetic Cardiomyopathy.

INTRODUCTION

The epidemic of obesity and sedentary lifestyle is projected to result in over 300 million people with diabetes mellitus by 2025[1]. Cardiovascular disease is responsible for 80%of deaths among diabetic patients much of which has been attributed to CAD (coronary artery disease). However, there is an increasing recognition that diabetic patients suffer from an additional cardiac insult termed diabetic cardiomyopathy. Diabetic cardiomyopathy refers to a disease process which affects the myocardium in diabetic patients causing a wide range of structural abnormalities eventually leading to LVH [left ventricular (LV) hypertrophy] and diastolic and systolic dysfunction or a combination of these. The concept of diabetic cardiomyopathy is based upon the idea that diabetes is the factor which leads to changes at the cellular level, leading to structural abnormalities as outlined above. It can be subclinical or apparent depending on the presence of symptoms and signs. There appears to be a long subclinical course in

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most patients before the development of symptoms[2].

Diabetic cardiomyopathy is common in both type 1 and type 2 diabetes[3]. The mechanisms of metabolic disturbances, myocardial fibrosis, microvascular disease, and insulin resistance in diabetic cardiomyopathy imply that various treatments might be effective for preventing or delaying the development of diabetic cardiomyopathy and its complications. These include improving diabetic control; use of calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, or related drugs; exercise training; lipid-lowering therapy; antioxidant and insulin-sensitizing drugs.

Cocos nucifera has been described as the "tree of life" or "tree of heaven" and nature's greatest gift to man. Each part of the coconut tree can be used to produce items of value for the community. It is a dominant type tree belonging to the family Arecaceae (palm). The common name of *Cocos nucifera* is coconut or coconut palm. The flowers of *Cocos nucifera* has potent therapeutic values like anti bacterial, larvicidal, antioxidant, dietary, antiinflamatory, hepatoprotective and anti cancer activity[4] but there is no literatures available for its antidiabetic activity and diabetic complications. Hence the present study was undertaken to investigate the protective effect of aqueous extract of *Cocos nucifera* flowers against diabetic cardiomyopathy in streptozotocin and doxorubicin treated rats.

MATERIALS AND METHODS

Collection of plant material

The flowers of *C. nucifera* were procured from the Pollachi, identified by Dr. G.V.S. Murthy, Botanical Survey of India, Tamilnadu Agricultural University (TNAU), Coimbatore and the voucher no is BSI/SRC/5/23/09-10/Tech-983.

Sample extraction

100g of dried flower powder was extracted in 500 ml of ethanol in an orbital shaker for 72hrs. Repeated extraction was done with the same solvent till clear colorless solvent was obtained. Obtained extract was evaporated and stored at 0-4^{o}C in an air tight container for further use.

Animals

The Wistar strain of albino rats weighing about 150-200 g were obtained from the animal house of Karpagam University, Coimbatore and used for the study. Rats were housed at constant temperature of 22+5°C with a 12-hour light, 12-hour dark cycle and fed on pellets with free access to tap water. All the experiments were carried out according to the guidelines recommended by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Government of India.

Induction of experimental diabetes and cardiomyopathy

Rats were rendered diabetic and cardiomyopathy by a single intraperitoneal injection of freshly prepared streptozotocin (45 mg/kg body weight) in 0.1M citrate buffer (pH 4.5) in a volume of 1ml/kg body weight and doxorubicin (1.5mg/kg body weight) in a volume of 4.5 units. Normal rats received 1 ml citrate buffer as vehicle.

Sample preparation

200 mg/kg of *C. nucifera* flower extract was weighed and mixed with water and given orally to control and experimental rats by using intragastric tube for 30 days.

Experimental Design

The rats were divided into 6 groups of five animals each. Group I served as control, group II consisted of normal rats treated with doxorubicin alone to induce cardiomyopathy (1.5 mg/kg body weight), group III consisted of streptozotocin-doxorubicin treated rats (45 mg/kg streptozotocin + 1.5 mg/kg doxorubicin); group IV consisted of doxorubicin-streptozotocin treated diabetic rats who received *C. nucifera* at a dose of 200 mg/kg, group V was doxorubicin and plant extract treated group, group VI consisted of doxorubicin treated rats who received aspirin (1.2 mg/kg).

Biochemical studies

The blood was obtained through tail puncture and biochemical tests were measured using electronic glucometer at a baseline, 15th and 30th days of treatment in fasting state. After 30 days of treatment the animals were sacrificed under chloroform anesthesia. The blood was collected, serum was separated and used for biochemical determination of glucose[5], urea, creatinine, total cholesterol, high density lipoprotein (HDL), very low density lipoprotein (VLDL), low density lipoprotein (LDL), triglycerides, lactate dehydrogenase (LDH), creatinine kinase, glutathione, serum glutamate oxaloacetate transaminase (SGOT) (AST), serum glutamate pyruvate transaminase (SGPT) (ALT) and alkaline phosphatase (SALP) by using kits. The athrogenic and coronary risk indices were calculated by using the following formula

AI = LDL/ HDL

CRI = TC/ HDL

Histopathological analysis

At the end of the study, the rats were sacrificed and pancreatic samples were also collected. The pancreatic tissues were fixed in 10% formalin immediately after removal from the animal to avoid decomposition. Embedding in paraffin wax was carried out by removal of water using alcohol and then stained with hemotoxylin, which has an aqueous base. The sections were dehydrated using increasing concentrations of alcohol and then stained with eosin. They were treated with diphenylxylene (DPX) and examined under the microscope.

Statistical analysis

Results were expressed as Mean + SD. Statistical significance was evaluated by One Way Analysis of Variance (ANOVA) using SPSS version (10.0) and the individual comparisons were obtained by the Duncan multiple range test (DMRT). A value of $p<0.05$ was considered to indicate a significant difference between groups.

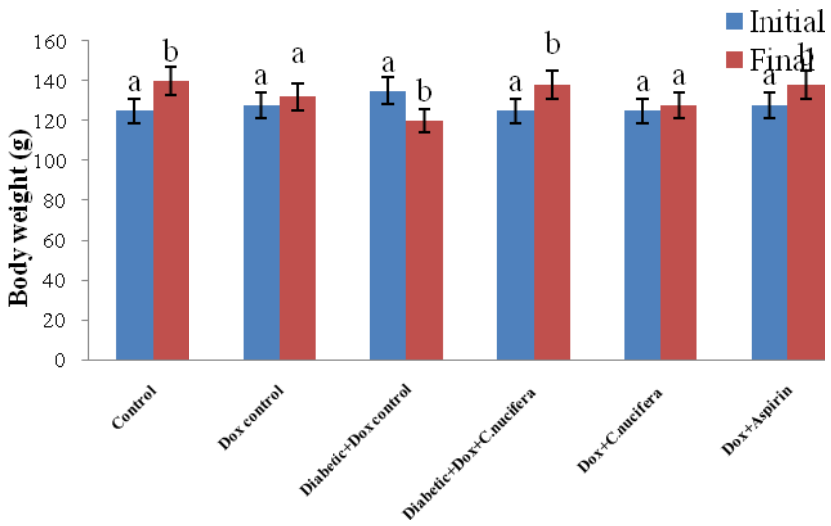
RESULT AND DISCUSSION

Cardiaomyocytes of diabetic patients were recognized to have an abnormal, energy-inefficient metabolic function, with almost no carbohydrate oxidation. In diabetes, metabolic remodeling precedes the cardiomyopathy[6], these changes may contribute to cardiac dysfunction. Impaired regulation of glucose utilization is a main feature of both type 1 and type 2 diabetes, and this contributes to cardiac dysfunction. Treating animal models with metabolic modulators at an early age, prior to any sign of cardiomyopathy, improved heart function[7]. Thus, it is evident that metabolic derangements seen in diabetic cardiomyopathy do not only precede the pathology, but also contribute greatly to its development[8].

Figure 1 shows the initial and final body weight of the normal and experimental groups, in which the rats in the streptozotocin and doxorubicin treated groups showed a significant decrease in the body weight. Induction of diabetes and cardiomyopathy by streptozotocin and doxorubicin leads to loss of body weight due to the increased muscle wasting and loss of tissue proteins[9]. Administration of aqueous *C. nucifera* for 30 days significantly increased the body weight when compared with group II and group III.

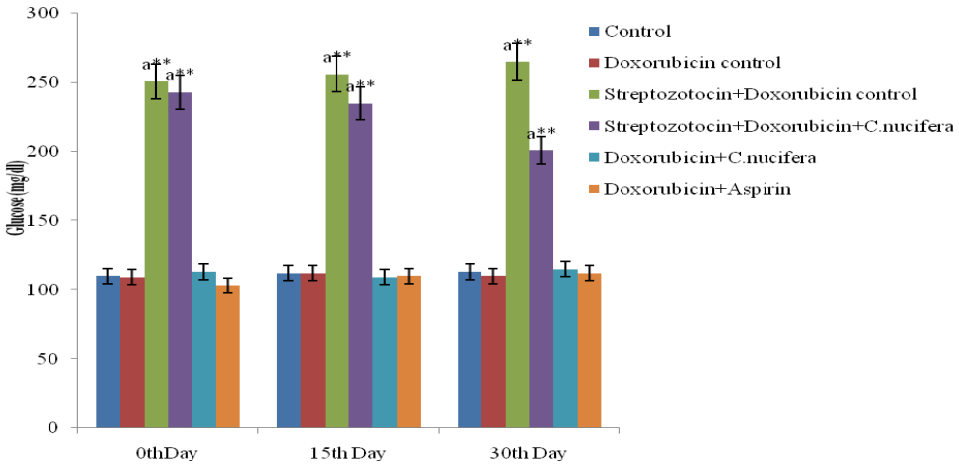
Figure 2 shows the levels of blood glucose of normal and experimental rats on 0, 15 and 30 days. There was a significant elevation ($p<0.05$) in blood glucose in streptozotocin-doxorubicin treated rats, when compared with normal rats. Administration of aqueous extract of *C. nucifera* for 30 days significantly reduced the blood glucose level when compared to streptozotocin-doxorubicin treated rats. There was no significant change of blood glucose in the doxorubicin - and aspirin- treated groups but there was a moderate increase in the glucose level in rats treated with streptozotocin-doxorubicin combination, which came back to normal after the treatment with *C. nucifera.* Increased endogenous glucose production is a common abnormality associated with diabetes that, in concurrence with deprived pancreatic function and reduced glucose clearance, contributes to the hyperglycemia characteristic of diabetes and this was

reflected in our study[10]. This results in the disruption of prooxidant/antioxidant balance[11], which can damage the pancreatic β cells and induce insulin resistance.



Values are expressed as mean ± S.D (n=5).

Figure 1: Effect of *C. nucifera* extract on body weight



Values are expressed as mean ± S.D. Values are taken as a mean of five individuals' experiments. a ** - Significance at $p < 0.05$

Figure 2. Effect of *C. nucifera* extract on concentration of blood glucose at various periods of the study

Table 1 shows a significant increase in serum urea and creatinine level in streptozotocin-doxorubicin-treated rats compared to the control. The administration of the aqueous extract of *C. nucifera* produced positive effect by

bringing down the level of urea and creatinine in streptozotocin-doxorubicin treated rats. Similar results were obtained in the aspirin-treated groups. As seen in the present study the level of renal function markers such as serum creatinine and urea was increased in streptozotocin-doxorubicin and doxorubicin alone treated rats indicating the dysfunction of kidney[12], which was reversed by the treatment with *C. nucifera.*

Table 1 Effect of *C. nucifera* extract on serum urea and creatinine

Experimental Groups	Urea (mg/dl)	Creatinine (mg/dl)
Normal	19±1.78^{a}	0.79±0.04^{a}
Doxorubicin	32.5±1.42^{e}	2.2±0.3^{b}
Streptozotocin+ Doxorubicin	42.5±1.08^{b}	2.75±0.31^{b}
Streptozotocin + Doxorubicin + *C. nucifera*	28±1.36^{f}	0.99±0.10^{a}
Doxorubicin + *C. nucifera*	25.2±0.85^{g}	1.0±0.22^{a}
Doxorubicin + Aspirin	20.5±1.21^{ac}	0.8±0.13^{a}

Values are expressed as mean ± SD (n=5). Values not sharing common superscript letters $^{(a-c)}$ differ significantly at p<0.05 (DMRT).

Table 2 Effect of *C. nucifera* extract on the concentration of AST, ALP and SALP

Experimental Groups	AST (IU/L)	ALP (IU/L)	SALP (IU/L)
Normal	124±2.36^{a}	84±2.25^{a}	260±1.36^{a}
Doxorubicin	290±2.25^{e}	200.2±1.35^{e}	350±1.36^{e}
Streptozotocin+ Doxorubicin	510±2.05^{g}	210.4±1.23^{e}	362±1.00^{e}
Streptozotocin + Doxorubicin + *C. nucifera*	150±1.78^{d}	126.6±1.03^{f}	280±1.69^{f}
Doxorubicin + *C. nucifera*	130±2.68^{f}	110±1.78^{c}	280±1.69^{d}
Doxorubicin + Aspirin	128±1.78^{af}	105±1.70^{g}	262±1.63^{a}

Values are expressed as mean ± SD (n=5). Values not sharing common superscript letters $^{(a-f)}$ differ significantly at p<0.05 (DMRT).

Table 2 shows that serum AST, ALT and SALP activities were significantly increased in streptozotocin-doxorubicin-treated group rats. Treatment with *C. nucifera* extract significantly reduced these values similar to aspirin. Elevated levels of AST, ALT and alkaline-phosphatase were reported in animals treated with

streptozotocin and doxorubicin[13, 14]. Transaminases are an important class of enzymes linking carbohydrates and amino acid metabolism, and these enzymes have a relationship between the intermediates of the tricarboxylic acid (TCA) cycle[15]. An increase in the AST, ALT and SALP activities was recorded in rats with diabetes and cardiomyopathy, indicating also altered liver function[16]. After *C. nucifera* extract treatment, there was reversal in the activation of these enzymes.

Table 3 also shows that the cardiac marker enzymes serum LDH and creatine kinase were increased while blood glutathione was reduced in rats treated with cardiotoxic agent doxorubicin. Isoproterenol administration produced myocardial necrosis in the heart as evidenced by a significantly increased serum LDH and creatine kinase and decreased blood glutathione[17]. LDH is often used as a marker of tissues breakdown as LDH is abundant in red blood cells and can function as a marker for hemolysis. A blood sample that has been handled incorrectly can show false-positively high levels of LDH due to erythrocyte damage. It can also be used as a marker of myocardial infarction[18].

Table 3 Effect of *C. nucifera* extract on the concentration of serum LDH, creatine kinase and glutathione

Experimental Groups	LDH (IU/L)	Creatinine kinase (mg/dl)	Glutathione (µg/mg protein)
Normal	92.7 ± 0.54^{ah}	61.74 ± 0.35^{a}	3.29 ± 0.4^{a}
Doxorubicin	130.3 ± 0.78^{f}	355.77 ± 0.97^{e}	1.10 ± 0.02^{b}
Streptozotocin+ Doxorubicin	101 ± 0.65^{g}	363 ± 0.43^{e}	1.00 ± 0.01^{b}
Streptozotocin + Doxorubicin + *C. nucifera*	96.5 ± 0.81^{g}	80.3 ± 0.90^{f}	3.08 ± 0.05^{b}
Doxorubicin + *C. nucifera*	90 ± 1.36^{a}	71.1 ± 1.32^{g}	2.56 ± 0.42^{e}
Doxorubicin + Aspirin	93.5 ± 0.73^{h}	73.4 ± 0.71^{h}	5.13 ± 0.48^{f}

Values are expressed as mean ± SD (n=5). Values not sharing common superscript letters $^{(a-f)}$ differ significantly at $p<0.05$ (DMRT).

Table 4 Effect of *C. nucifera* on the lipid profile

Experimental Groups	Total cholesterol (mg/dl)	TGL (mg/dl)	LDL (mg/dl)	HDL (mg/dl)	VLDL (mg/dl)
Normal	125 ± 1.78^{a}	70 ± 1.78^{a}	86 ± 1.23^{a}	52 ± 0.95^{a}	14 ± 1.23^{a}
Doxorubicin	213 ± 1.42^{e}	210.5 ± 1.7^{f}	128.6 ± 1.00^{f}	27.3 ± 1.30^{b}	42.1 ± 1.35^{d}
Streptozotocin+ Doxorubicin	252 ± 0.82^{b}	235 ± 1.25^{b}	151 ± 1.10^{b}	22.2 ± 1.21^{a}	49.2 ± 1.30^{b}
Streptozotocin + Doxorubicin + *C. nucifera*	168 ± 1.40^{f}	100.1 ± 1.3^{g}	121.1 ± 1.42^{d}	20.4 ± 1.25^{e}	40.0 ± 1.28^{d}
Doxorubicin + *C. nucifera*	146 ± 1.20^{g}	89.9 ± 1.44^{h}	143.5 ± 1.44^{e}	35.3 ± 1.25^{cd}	37.8 ± 1.19^{e}
Doxorubicin + Aspirin	132 ± 0.83^{h}	76.3 ± 1.32^{c}	91.29 ± 1.43^{a}	42.4 ± 1.35^{fc}	30 ± 1.00^{c}

Values are expressed as mean ± SD (n=5). Values not sharing common superscript letters $^{(a-f)}$ differ significantly at $p<0.05$ (DMRT).

The doxorubicin-treated rats showed an increases LDH, creatinine kinase activity and decreased the glutathione concentration when compared to normal rats and the activities were reached near to normal leval in

doxorubicin- *C. nucifera* treated rats which confirms that the aqueous extract of *C. nucifera* has the ability to control cardiac toxicity. Administration of streptozotocin-doxorubicin administration caused a significant increase in creatinine kinase activity. The administration of *C. nucifera* extract significantly reduced the enzyme activity similar to the standard drug aspirin. The doxorubicin and streptozotocin-doxorubicin induced group rats showed an increased level of total cholesterol, TGL, LDL, VLDL and which were found to decreased in *C. nucifera* treated rats. The HDL was reduced in the streptozotocin-doxorubicin -treated animals and increased in rats that received *C. nucifera* extract (Table 4).

Table 5 Effect of *C. nucifera* on the athrogenic and coronary risk indices

Experimental Groups	Athrogenic Index (mg/dl)	Coronary Risk Index (mg/dl)
Normal	1.65±0.032[a]	2.40±0.044[a]
Doxorubicin	4.71±0.049[e]	7.80±0.045[e]
Streptozotocin+ Doxorubicin	6.80±0.055[f]	11.3±0.067[f]
Streptozotocin + Doxorubicin + *C. nucifera*	5.93±0.040[b]	8.23±0.067[g]
Doxorubicin + *C. nucifera*	4.06±0.040[g]	4.13±0.053[h]
Doxorubicin + Aspirin	2.15±0.036[h]	3.11±0.062[i]

Values are expressed as mean ± SD (n=5). Values not sharing common superscript letters [(a-j)] differ significantly at $p<0.05$ (DMRT).

An abnormality in lipid profile is one of the most common findings in diabetes mellitus and cardiomyopathy. A variety of derangements in metabolic and regulatory mechanisms, due to insulin deficiency, are responsible for the observed accumulation of lipids. It is well known that in uncontrolled diabetes mellitus, there will be an increase in total cholesterol, triglycerides and LDL cholesterol associated with decrease in HDL cholesterol[19]. Hyperlipidemia certainly contributes to major risk factor for cardio vascular diseases[20]. Significant lowering of total cholesterol and rise in HDL-cholesterol is a very desirable biochemical state for preventing atherosclerosis and ischemic conditions[21] because high level of TC and LDL are major coronary risk factors[22]. Furthermore, the studies suggested that TG itself is independently related to coronary heart disease[23, 24]. The abnormalities in lipid metabolism lead to elevation in the levels of serum lipid and lipoprotein that in turn play an important role in occurrence of premature and severe atherosclerosis seen in patients with diabetes[25] Since lipid abnormalities accompanying atherosclerosis are the major cause of cardiovascular disease in diabetes, the ideal treatment of diabetes, in addition to glycemic control, should have a favorable effect on lipid profiles. Our results are similar to those of Adeneye et al. 2009[26], who showed that the aqueous seed extract of *Carica papaya* administered for 30days produced hypolipidimic effect.

The increase in the atherogenic index (AI) and coronary risk index (CRI) in the doxorubicin and streptozotocin-doxorubicin treated rats reflect the increased risk of heart disease. Both indices were reduced in the *C. nucifera* extract treated group rats. The standard drug aspirin also reduced both the AI and CRI (Table 5). Our data indicate the protective effect of *C .nucifera* on the heart. It is known that streptozotocin destroys insulin-secreting β-cells in the islets of Langerhans and its effect is irreversible. The ultrastructure of streptozotocin

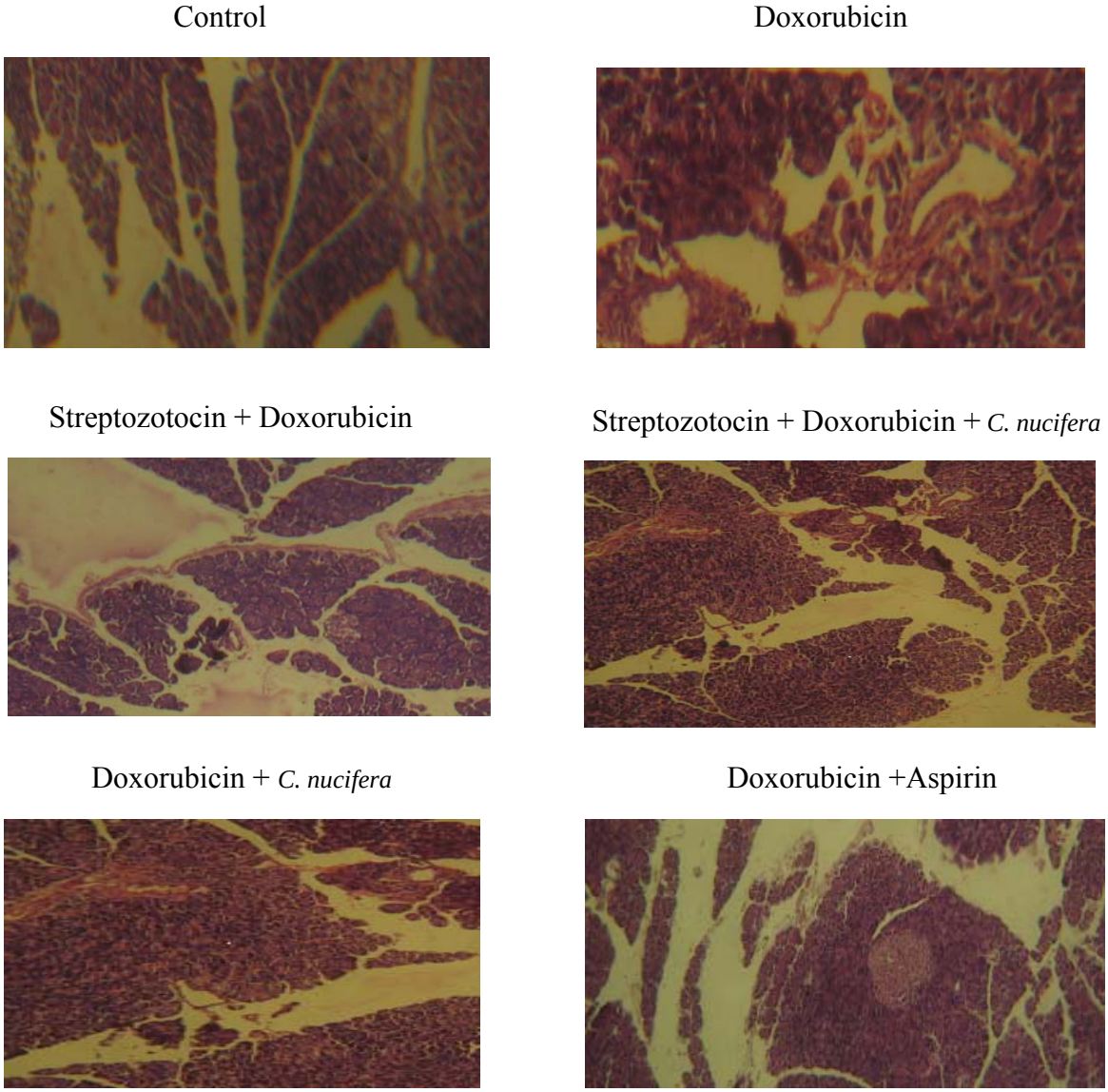


Figure 3 Histopathology of rat pancreas

diabetic pancreas showed considerable reduction in the islet of Langerhans and depleted islets[27]. There was a destruction of pancreatic β-cell in animals treated with streptozotocin-doxorubicin, when compared to control. This destruction was reversed by the administration of *C. nucifera* in streptozotocin-doxorubicin group rats (Figure 3) which coincided with reduction in blood glucose level.

CONCLUSION

The data obtained from the study showed the reduction of abnormalities in glucose and lipid metabolism as well as in cardiac and other metabolic parameters in rats with experimentally-induced diabetic cardiomyopathy Thus, aqueous plant extract of *Cocos nucifera* may be used in the treatment of diabetes mellitus and prevention of its complications.

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Conflict of Interest Statement

We declare that we have no conflict of interest.

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التأثير العلاجي للمستخلص المائي من كوكوس نوسيفيرا في بالستربتوزوتوسين – دوكسوروبيسين يسببها نموذج الفئران من السكري اعتلال عضلة القلب

بهوفانيشواري ونارمادها وجوماثي وكاليسيلفي وديفاكي[1]

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ملخص

مرض السكري هو واحد من الأمراض الأكثر شيوعا في اضطرابات الغدد الصماء، ويشكل تحديا خطيرا على الرعاية الصحية في جميع أنحاء العالم. مدى انتشار مرض السكري يختلف في أجزاء مختلفة من العالم. في مرضى السكري، التغير في التمثيل الغذائي يسبق اعتلال عضلة القلب، في هذه الدراسة، تم تحقيق من آثار مستخلص زهرة كوكوس نوسيفيرا (Cocosnucifera) على ضعف القلب أثناء مرض السكري.

الأساليب والنتائج: تم إعطاء مستخلص الزهرة المائي من زهرة كوكوس نوسيفيرا لمدة 30 يوما، وتمت مراقبة الفئران التجريبية. بعد ذلك تمت التضحية بالحيوانات، واستخدمت عينات الدم لتحليل السكر في الدم واليوريا والكرياتينين، والانزيمات المعلمة، وتحليل الدهون، وتحليل الأنسجة وتم أيضا فحص أنسجة البنكرياس. وأظهرت النتائج أن تحريض اعتلال عضلة القلب في مرضى السكري بالستربتوزوتوسين– دوكسوروبيسين سبب زيادة مستوى الجلوكوز، والانزيمات المعلمة لاعتلال القلب ورفع مستويات الدهون. استخدام المستخلص المائي لكوكوس نوسيفيرا لفئران التجارب خفض مستويات السكر والدهون واستعادة نشاط الإنزيمات إلى المستوى الطبيعي. وأظهر تحليل الأنسجة استعادة البنكرياس لهيكله في الحيوانات المعالجة بمستخلص الزهرة المائي من زهرة كوكوس نوسيفيرا بعد استخدام الستربتوزوتوسين– دوكسوروبيسين. زادت مؤشرات المخاطر وathrogenic التاجية بشكل ملحوظ في مجموعات الحيوانات التي تم إحداث السكري فيها عن طريق الستربتوزوتوسين–دوكسوروبيسين او دوكسوروبيسين. هذا وقد تم تخفيض هذه الاعتلال باستخدام مستخلص الزهرة المائي من زهرة كوكوس نوسيفيراوكذلك في الفئران المعالجة بالأسبرين ($p<0.05$). نستنتج أن التغذية باستخدام مستخلص الزهرة المائي من زهرة كوكوس نوسيفيرا للفئران المصابة بالسكري مع اعتلال عضلة القلب تحمي أنسجة القلب من مضاعفات مرض السكري .

الكلمات الدالة: كوكوس نوسيفيرا، ستربتوزوكوسين، ضعف القلب أثناء مرض السكري.

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