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# Effect of Abscisic Acid on Diabetic Cardiomyopathy in Streptozotocin-Nicotinamide-Induced Diabetic Rats

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## Abstract

The present study was performed to find out the possible protective effect of abscisic acid (ABA) against diabetic cardiomyopathy (DCM) in type II diabetic rats. **Materials and methods:** Fifty adult male albino rats were divided into five equal groups: normal control group, diabetic group, diabetic group treated with glibenclamide, diabetic group treated with ABA, and diabetic group treated with both glibenclamide and ABA in combination for 4 weeks. At the end of the experiment, ECG, heart weigh and HW/BW ratio was recorded, biochemical measurement of diabetic markers (serum glucose, insulin and calculated HOMA-IR); cardiac enzymes (cardiac troponin I, CK-MB, and LDH);oxidative stress markers in the heart (MDA and catalase) and histopathological examination of cardiac tissue.**Results**: Treatment with ABA exerted positive effects on blood glucose, insulin levels, and insulin resistance that were found to be reflected on heart weight/body weight ratio and ameliorate the histological morphology of the heart in diabetic rats. Also, it exerted significant improvement in cardiac enzymes and stress markers. DCM was associated with prolongation of QTc. **Conclusion:** The diabetic rats benefit from ABA intake due to its hypoglycemic, anti-inflammatory, antioxidant, anti-fibrotic, and anti-apoptotic effects or through nitric oxide production improving cardiac perfusion. So, intake of ABA in combination with anti-diabetic drugs may be beneficial for type II diabetic patients.

**Keywords: (**Abscisic acid, diabetic cardiomyopathy, oxidative stress, and anti-diabetic drug).

## Introduction

Cardiovascular complications due to long-term uncontrolled hyperglycemia are considered one of the leading causes of morbidity and mortality among diabetic patients.[1]Long-term diabetes promoted cardiac dysfunction; a condition called diabetic cardiomyopathy (DCM), either directly or indirectly. DCM is induced directly through up-regulation of calpain-1 in mitochondria that induce the cleavage of ATP synthase, increase in superoxide generation, and apoptosis in cardiomyocytes.[2] In addition, increased formation of myocardial advanced glycation end-products (AGEs) that promote collagen accumulation followed by fibrosis in the cardiac tissue.[3] DCM induced indirectly through atherosclerosis.[4]The risk incidence of

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occurring heart failure increases in diabetic patients regardless hypertension, hyperlipidemia, obesity, or underlying coronary heart disease.[5]

The character of DCM isa dysfunction ofsystole and diastole, as a result of some factors like oxidative stress, inflammatory process, apoptosis, and myocardial fibrosis.[6]

Abscisic acid (ABA) is a phytohormone founds in fruits and dietary vegetables like figs, potato, soy milk, apple, apricot, banana, and olive and is involved in the regulation of the physiological process of plants. ABA is called the 'stress hormone' as it controls many features of plant growth under different stress conditions.[7]

Abscisic Acid (ABA) is one of the human endogenous hormones and produced by various cells (pancreatic β-cells,leukocytes, stem cells, and fat cells).[8]ABA has a role in the regulation of glucose homeostasis by stimulating insulin and GLP-1secretions and peripheral glucose uptake.[9]

ABAstimulates target cells through activation of lanthionine synthetase C-like protein 2 (LANCL2) leading to an increase of the intracellular cAMP and calcium that mediated its effects.[10]LANCL-2 has been proposed as a therapeutic target in the treatment of diabetes and inflammatory diseases.[11]

Moreover, an in vitro previous study suggested a protective role of endogenous ABA against oxygen depletion in cardiomyocytes, through stimulating glucose uptake and nitric oxide (NO) production. So, the present study was performed to find out the role of abscisic acid in glycemic control of type II DM and its possible protective roleagainst diabetic cardiomyopathy.[12]

## Material and methods

### *Chemicals*

Streptozotocin (STZ), nicotinamide, and ABA were purchased from Sigma-Aldrich Co., St Louis, USA.Glibenclamide (Gliben) oral antidiabetic drug purchased from Sanofi Aventis pharmaceutical industries, Egypt.

### *Experimental animals*

Fifty adult male rats albino of local strain, with average body, weighs between 110-130g were included in the study. Animals were bred and housing in the animal house of the Medical physiology department, Al-Azhar University. They were kept in suitable cages (30x32x30 cm for every five rats) on natural light/dark cycle andat room temperature.The animals were provided with water ad libitum and food pellets during the period of the studyexcept when starvation was required.They were kept for one week for the adaptation to the new environment.

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***Induction of diabetes***

To induce experimental type II DM in rats, nicotinamide (100 mg/ kg) was injected intraperitoneally (i.p), followed by streptozotocin injection (55 mg/kg, i.p) after 20 minutes. Nicotinamide and streptozotocin were dissolved in 0.9% normal saline and citrate buffer (pH 4.5), respectively. On day 7, following STZ administration, the level of fasting blood glucose was measured by collecting whole blood from the tail vein. Rats that had fasting glucose level more than 250 mg/dl were considered diabetic. The blood glucose level was measured using an Accu-Chek glucometer (Roche, Germany). [13]

***Experimental design***

Rats were randomly divided into five groups (n=10 in each group): group I: served as a normal control group; group II: served as a diabetic control;group; III: Diabetic rats received glibenclamide (0.6 mg/kg body wt) daily by oral gavage for 4 weeks **[14];**groupIV:Diabetic rats received abscisic acid ((1 mg/kg body wt) daily by oral gavage for 4 weeks**[15]**and group V: Diabetic rats received both glibenclamide and abscisic acid with the same previous doses for 4 weeks. After one month of treatment, ECG was recorded. Rats were fastedovernight, then anesthetized to collect a blood sample from the retro-orbital venous plexus which allowed to clot. Serum was separated by centrifugation and stored at -20 ˚C until biochemical analysis. After blood sampling, rats were weighed and immediately euthanized and each rat heart was excised, cleaned, and weighed. Finally, part of heart tissue was homogenized for biochemical assay, while another part of cardiac tissue was fixed in 10% formalin for histological studies.

***ECG recording***

ECG was recorded twice, the first one at the beginning of the study to exclude any cardiac abnormality and the second at the end of the study.Briefly,rats wereanesthetized with ketamine (100) mg/kgi.p), and ECGs were recorded using Biopac MP 35 data acquisition system (Biopac system, Canada) throughneedle electrodes inserted under the skinof the animals at lead II position.

***Biochemical analysis of serum and cardiac tissue homogenate***

Serum glucose level (mg/dl) wasestimated usingcommercial kits provided byBio Diagnostics( Giza, Egypt), and insulin level (μU/ml) was estimated according to previous studyusing a radio immune assay (RIA) kit provided by (Sigma -Aldrich, St Louis, MO, USA).**[16]**Insulin resistance was calculated using the HOMA-IR model as HOMA-IR = Fasting glucose (mg/dl) x fasting insulin (μU/ml)/405. **[17]**Serum levels of cardiac troponin I, CK-MB, and LDHwere estimated according to the standard methods using ELISA kits purchased from RayBiotech (Norcross, GA, USA).Catalase and MDA in heart tissue were measured using colorimetric kits purchased from BioDiagnostics (Giza, Egypt).

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***Heart weight/body weight ratio***

After euthanasia, a rat was weighed then the heart was isolated, dried, and weighed, and the heart/body weight (HW/BW) ratio was calculated to evaluate the cardiac hypertrophy degree.[18]

***Histopathological examination***

Parts of the isolated heart were taken and preserved in 10% formalin. All specimens were paraffin-embedded, sectioned at5 μm thin sections, and were stained with hematoxylinand eosin and Masson's trichrome for staining collagen fibers.

***Statistical analysis***

All our descriptive data are presented as the mean ± SD for each group. Data were analyzed using one-way ANOVA followed by post-hoc Tukey's test to evaluate the significance between the different groups using SPSS version 20(IBM Co., USA). Value with $P \leq 0.05$ was considered significant.

**Results**

***Body weights and HW/BW ratio (table1)***

Diabetic rats showed a significant body weight loss as compared to normal control rats. When diabetic rats were treated with ABA or glibenclamide for one month, their body weight was significantly higher than bodyweight of diabetic control rats. Also, body weight was significantly higher in combined treated group compared to either diabetic or glibenclamide treated group or ABA treated group

Regarding HW/BW ratio, diabetic control group revealed a significant elevation in HW/BW ratio as compared to control one. However, HW/BW ratio was significantly reduced in all diabetic treatedgroups when compared to diabetic control one. Also, HW/BW ratio was significantly decreased in combined treated group compared to glibenclamide or ABA treated groups.

***Blood glucose, insulin, and HOMA-IR levels (table1)***

As regard glucose, level of blood glucose was significantly higher in type II diabetic group than in normal group. On the other hand, level of glucose was significantly lower in either glibenclamide or ABA or combined treated groups when compared to diabetic group. Also, glucose was significantly lower in combined treated group compared to glibenclamide-treated group.

As regard insulin, insulin level was significantly lower in diabetic group than in normal group. On the other hand, insulin was significantly higher in glibenclamide or ABA-

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treated diabetic rats than its level indiabetic control rat. Also, insulin was significantly higher in combined treated group compared to either diabetic or glibenclamide treated groups.

Regarding HOMA-IR,it was significantly higher in diabetic group as compared to normal group. On the other hand, HOMA- IR was significantly lower in glibenclamide and ABA treated groups compared to diabetic group. Also, HOMA- IR was significantly lower in combined treated group compared to diabetic group.

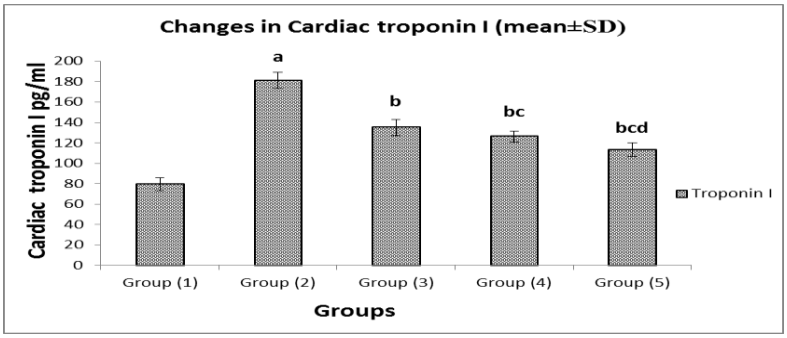
**Tables (1)** Effect of abscisic acid and glibenclamide supplementation on body weight, HW/BW ratio, and diabetic markers (glucose, insulin HOMA-IR) levels in various studied groups.

| | Group (I) control | Group (II) DM | Group (III) DM+gliben | Group (IV) DM+ABA | Group (V) DM+gliben+ABA |
|---|---|---|---|---|---|
| BW(gm) | 410.8±15.3 | 306.3±7.4$^{a}$ | 362.2±7.7$^{b}$ | 371.3±7.9$^{b}$ | 403. 0±11$^{bcd}$ |
| HW/BW(mg/g) | 1.66±0.04 | 1.86±0.09$^{a}$ | 1.69±0.03$^{b}$ | 1.58±0.04$^{b}$ | 1.36±0.02$^{bcd}$ |
| Glucose(mg/dl) | 111.7±3.6 | 349.2±25.8$^{a}$ | 191.7±10.8$^{b}$ | 167.3±7.9$^{b}$ | 144.2±16. 6$^{bc}$ |
| Insulin(µU/ml) | 20.6±3.1 | 9.7±1.3$^{a}$ | 15.9±0.9$^{b}$ | 17.9±0.9$^{b}$ | 18.5±0.7$^{bc}$ |
| HOMA-IR | 5.7±0.8 | 8.4±1.7$^{a}$ | 7.6±0.7$^{b}$ | 7.4±0.5$^{b}$ | 6.6±0.7$^{b}$ |

Data were expressed as mean ± SD, P: significance ≤0.05; a: significance as compared to control group, b: significance as compared to DM group, c: significance as compared to DM+gliben. group, d: significance as compared to DM+ABA group. DM, diabetes mellitus; ABA, abscisic acid; HW/BW, heart weight/body weight;HOMA-IR,homeostasis model assessment of insulin resistance.

***Cardiac biomarkersFigure (1)***

Levels of cardiac troponin I, CK-MB, and LDH were significantly higher in diabetic group than in normal group. On the other hand, levels of these enzymes were significantly lower in either glibenclamide, ABA, and combined treated groups when compared with diabetic control group. Also, cardiac troponin I, CK-MB, and LDH levels were significantly lower in combined treated group compared to glibenclamide or ABA diabetic treated groups.



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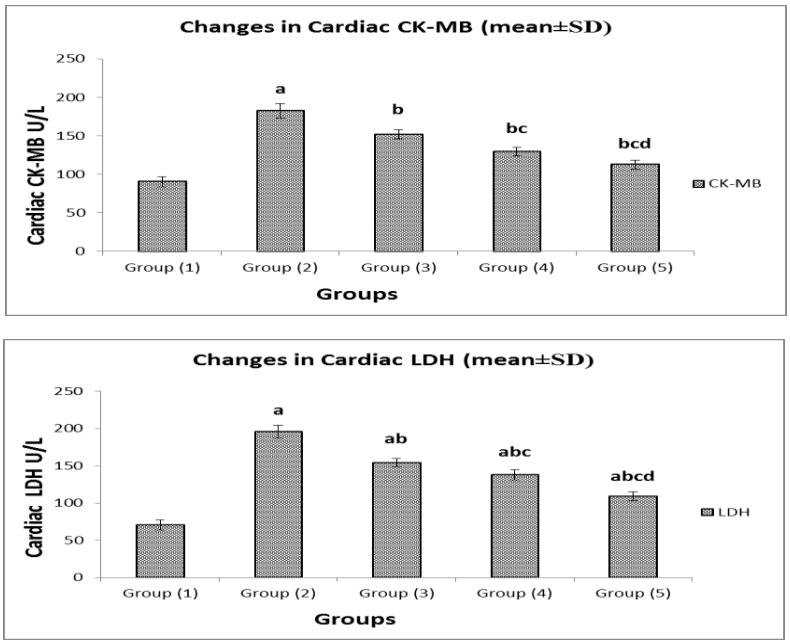


**Fig. (1)** Effect of abscisic acid and glibenclamide supplementation on cardiac enzyme markers at various studied groups. Data are expressed as mean ± SD, P: significance ≤0.05; a: significance as compared to control group, b: significance as compared to DM group, c: significance as compared to DM+glibenclamide group, d: significance as compared to DM+ABA group. DM, diabetes mellitus; ABA, abscisic acid.

## *ECG table (2), figure (2)*

QTc interval was significantly prolonged in diabetic group compared to normal group, on the other hand, QTc interval was significantly shortened in ABA, glibenclamide, and combined treated diabetic groups compared to diabetic control group and there were non-significant changes in other parameters of ECG, also QTc interval was significantly shortened in combined treated group compared to glibenclamide treated group.

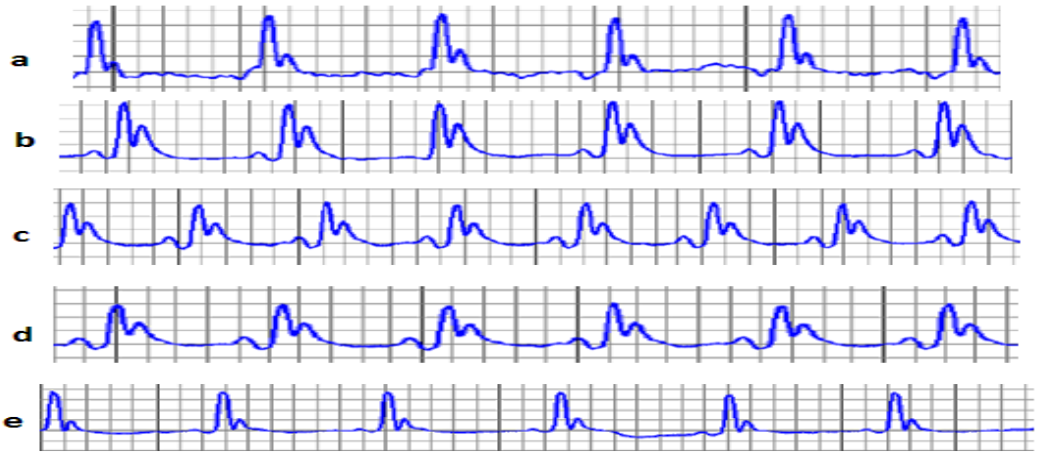


**Fig. (2; a, b, c, d, and e):** ECG tracing of different studied groups; **a;** ECG of lead II in groupI, **b;** ECG of lead II in group II,**c;** ECG of lead II in groupIII,**d;** ECG of lead II in group IV,**e;** ECG of lead II in group V.

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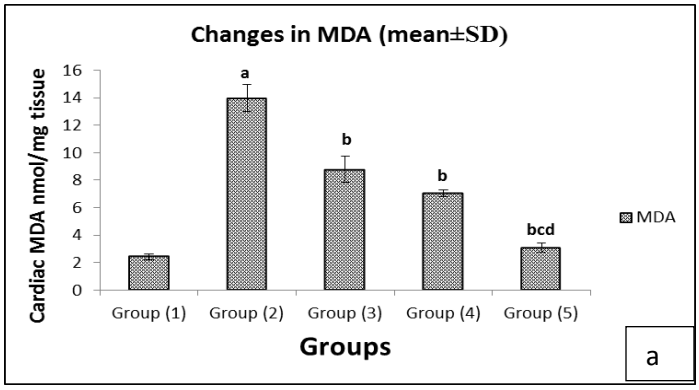
**Tables (2)** Effect of abscisic acid and glibenclamide supplementation on some ECG parameters in the various experimental groups.

| | Group (I) control | Group (II) DM | Group (III) DM+gliben | Group (IV) DM+ABA | Group (V) DM+gliben+ABA |
|---|---|---|---|---|---|
| HR (bpm) | 246±8.84 | 220±13.6 | 225±9.83 | 278±11 | 263±19 |
| QRS duration(sec) | 0.038±0.004 | 0.042±0.004 | 0.037±.005 | 0.038±0.004 | 0.035± 0.005 |
| QRS amplitude(mv) | 0.313 ±0.05 | 0.327±0 .05 | 0.253±0.05 | 0.230±0.07 | 0.262 ±0.08 |
| QTc interval(sec) | 0.062±0.024 | 0.089±0.017[a] | 0.069±0.023[b] | 0.073±.033[b] | 0.066±.041[bc] |
| ST segment elevation (mv) | 0.010±0.008 | 0.028±0.038 | 0.027±0.020 | 0.003±0.005 | 0.022±0.038 |

Data are expressed as mean ± SD, P: significance ≤0.05; a: significance as compared to control group, b: significance as compared to DM group, c: significance as compared to DM+gliben. group, d: significance as compared to DM+ABA group. DM, diabetes mellitus; ABA, abscisic acid; Pbm, beat per minute.

***Oxidative stress and antioxidant marker figure (3)***

Level of MDA was significantly higher in diabetic than in normal control group. On the other hand, level of MDA was significantly lower in glibenclamide, ABA, and combined treatment group when compared with diabetic group. Also, MDA was significantly lower in combined treatment group thanABA orglibenclamide treated group. Level of catalase was significantly lower in diabetic groupthan in normal diet group. On the other hand, level of catalase was significantly higher in either glibenclamide treated group, ABA treated group, and combined treated groupswhen compared with diabetic group. Also, catalase was significantly higher in combined treated group compared to glibenclamide or ABA treated group.



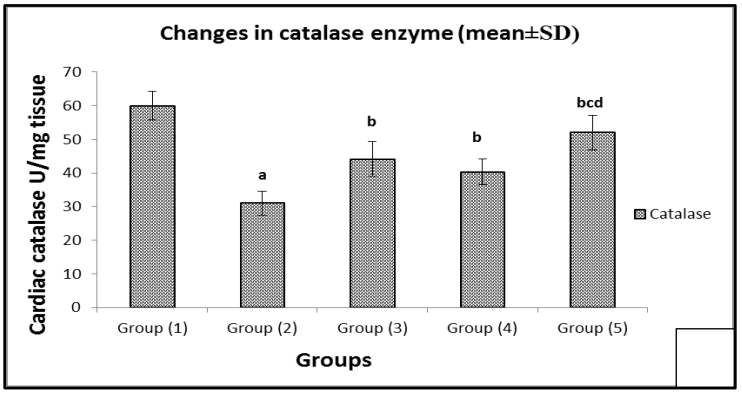




**Fig. (3; a and b)** Effect of abscisic acid and glibenclamide supplementation on MDA and catalase at various studied groups. Data are expressed as mean ± SD, P: significance ≤0.05; a:

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significance as compared to control group, b: significance as compared to DM group, c: significance as compared to DM+gliben. group, d: significance as compared to DM+ABA group. DM, diabetes mellitus; ABA, abscisic acid; MDA, malondialdehyde.

## *Histopathological examination*

**A- Myocardial morphologyassessment (hematoxylin and eosin stain) (Figure 4a-e)**

Heart specimen of control rat showed that myocardial fibers were arranged regularly, myocardial nuclei were clear, and myocardial gap was normal. Heart specimen of diabetic rats shows marked degeneration and separation of myocardial muscle fibers with marked inflammation & congestion in the blood vessel.In the diabetic animal treated with gliben, myocardial damage and separation were mildly ameliorated compared with diabetic group but blood vessels were still marked congested. In diabetic animals treated with ABA, the degeneration and separation of myocardial muscle fibers were ameliorated comparing to diabetic rats with minimal lymphocytic infiltration & blood vessel congestion. When diabetic rats were treated with ABA and gliben in combination, myocardial muscles separation and lymphocytic infiltration were minimal without degeneration near normal.

**B-Myocardial fibrosis assessment (Masson trichrome staining)**: **Figures (5a-e)**: Masson's trichromestaining shows collagen fibers (blue) and cardiomyocytes(red).Hearts of control animalsshowed no evidence of collagen deposition. Hearts ofdiabetic animals showed collagen fibers proliferation.Diabetic animals treated with gliben showed decreasecollagen proliferation compared to diabetic rats. Diabetic rats treated with ABA revealed focal fibrosis compared with diabetic group. When diabetic rats were treated with ABA and gliben in combination, the collagen fiber deposition was minimal compared to diabetic rats.

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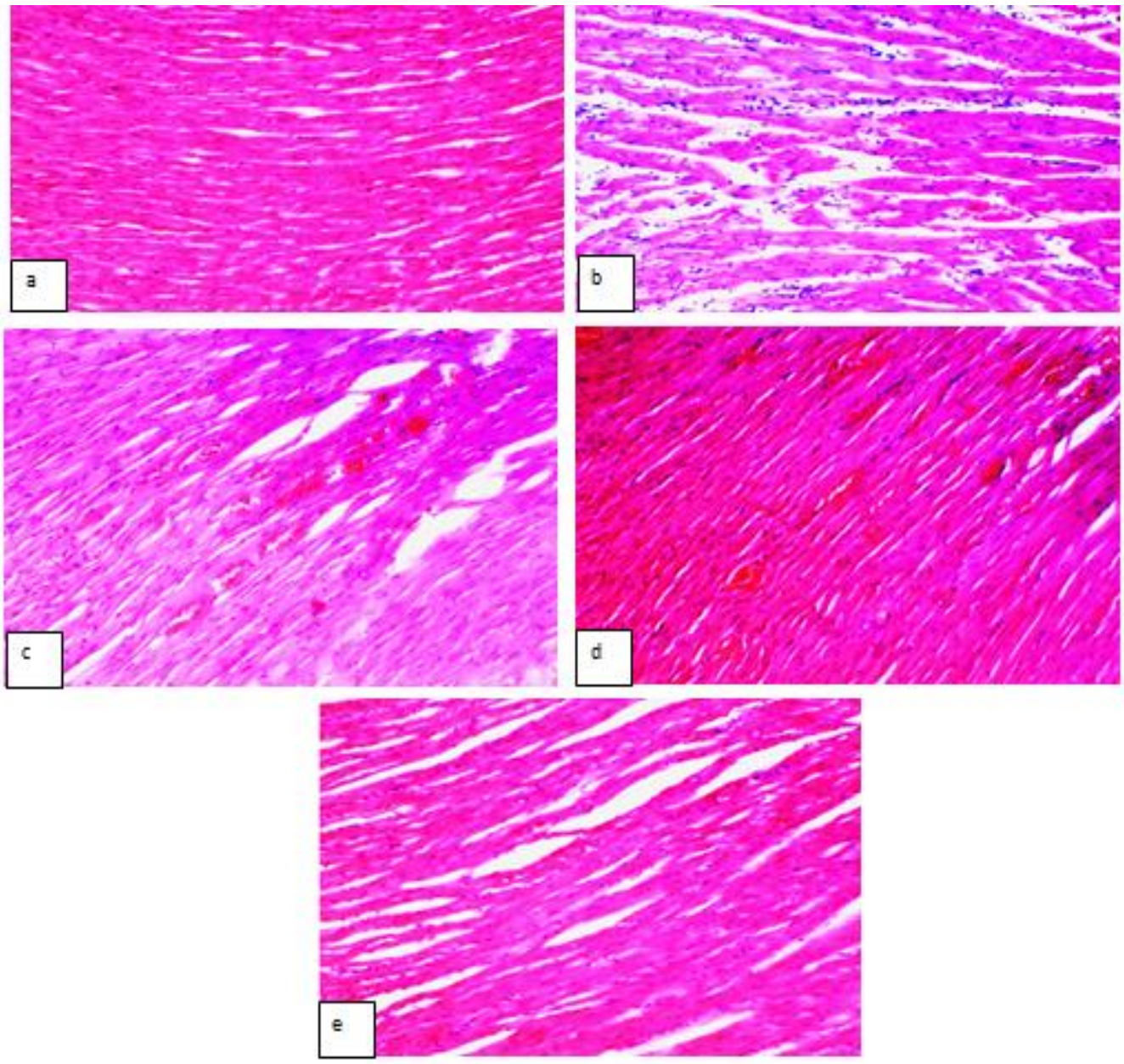


**Fig.(4)**: Heart specimens of the studied groups stained with H&E, (500px). (a) heart specimen of control rats shows normal myocardial fibers, (b) heart of diabetic rat shows myolysis, marked degeneration and separation of muscle fibers with marked inflammation & congestion of vessels,(c)heart of diabetic rat treated with gliben shows moderate degeneration & separation of fibers with marked congestion in vessels, (d) heart of diabetic rat treated with ABA shows minimal degeneration and separation of fibers with minimal lymphocytic infiltration & congestion, and (e) heart of combined treatment group shows minimal myocardial muscles separation without degeneration, minimal inflammation; near normal.

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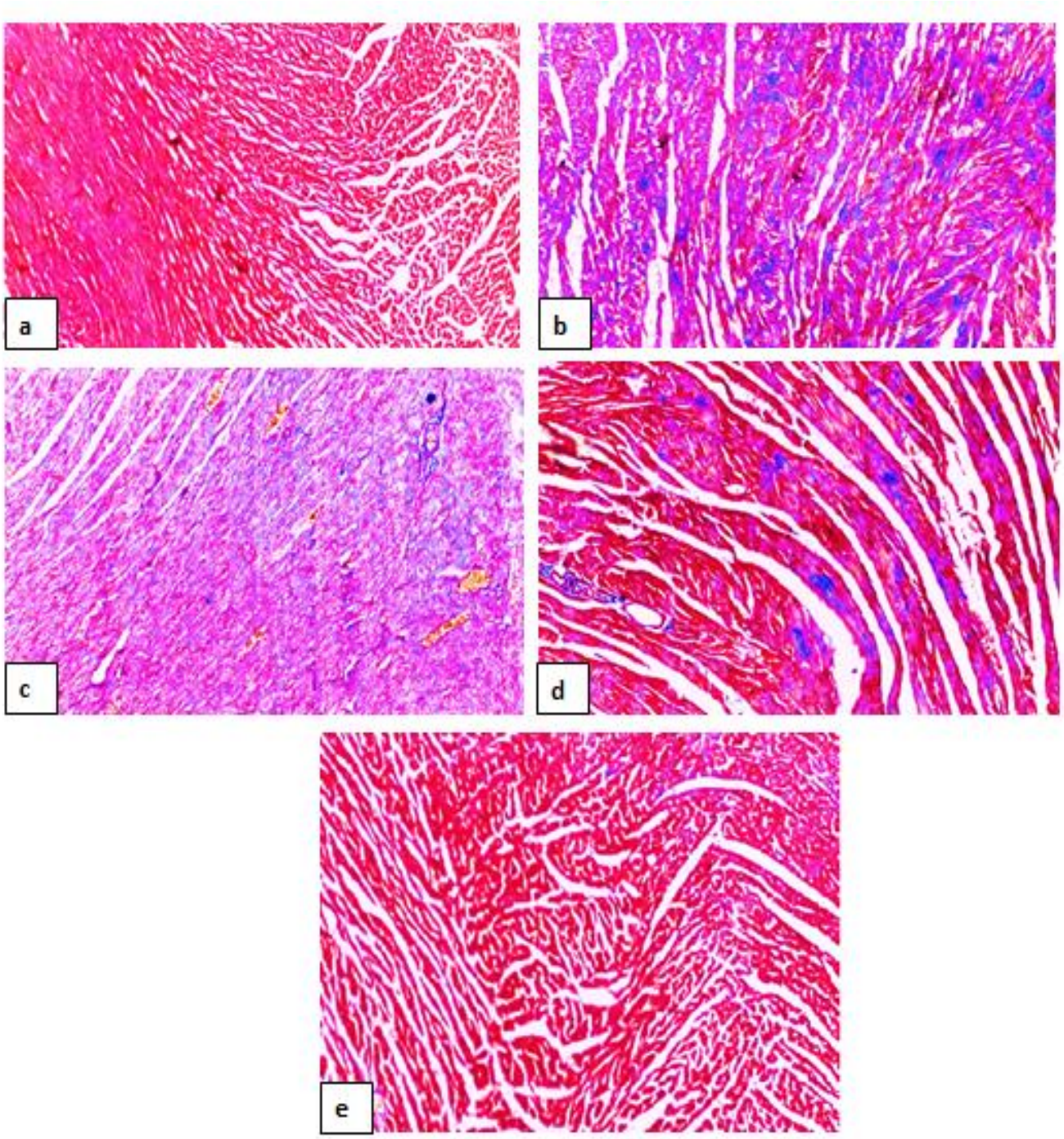


**Fig. (5):** Heart specimens of the studied groups stained with Masson trichrome stain (500px).(a) Heart of control animals shows no evidence of fibrosis, (b) heart of diabetic rat shows severe myolysis accompanied with advanced collagenfibers proliferation, (c) heart of diabetic rattreated with gliben shows mild interstitial collagen fibers between myocardial fibers, (d) heart of diabetic group treated with ABA shows focal collagen deposition and (e)

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heartof combined treatment group showsmarked decrease collagen fibers between myocardial fibers.

**Discussion**

Type II DM was induced by nicotinamide administration followed by a low dose of STZ. This is one of modelswhich used to study diabetic complication like; cardiomyopathy and neuropathy**.**[19]

Untreated diabetic group showed a significant elevation of serum glucose level, and (HOMA-1) in comparison to normal group, this finding was associated with a significant decrease in insulin level.HOMA-IR provides an exact estimation of insulin sensitivity in rats [20] andthese findings are consistent with another study. [21]

Treatment with abscisic acid exerted positive effects on serum glucose and HOMA-IR. In line with these data, a recent study observed that ABA stimulates glucose uptake via activation of AMP-dependent kinase (AMPK) and stimulates the expression of browning genes in the white adipose tissue, and increases glucose uptake in brown adipose tissue.[22]Also, the result was in harmony with another study which found that ABA stimulated insulin release through activation of $Ca^{2+}$ mobilizing second messenger cyclic ADP-ribose (cADPR), which is involved in insulin release from the pancreas.[23] The daily intake of 1 µg/Kg body weight of ABA for 75 days significantly improved fasting glucose level, glycated hemoglobin, and total cholesterol, triglyceride, and HDL levels in prediabetic patients**.**[24]Several observations suggested there was a positive feedback mechanism between ABA and GLP-1 which regulates glucose homeostasis, as ABA can stimulate GLP-1 release and GLP-1can stimulates ABA release from β cells**.**[9]

In the present study, the bodyweight of type II DM rats was significantly lower than those of non-diabetic rats. The previous findings were in agreement with previous studywhich reported that diabetes caused by STZ was associated with weight loss.[25] Aformerstudy in2016 found that insufficient insulin in diabetic patients results in the prevention of the body from getting glucose as an energy source, so, the body starts burning fat for getting energy, reducing the body weight. [26]

Treatment of diabetic rats with ABA and /or glibenclamide, the body weight was increased. This finding was in disagreement with another study which observed that abscisic acid stimulates the browning of white adipose tissue and increases activity of brown adipose tissue which could be the cause of body weight loss in chronically ABA-treated mice.[27]Also, the finding was in disagreement with a previousstudy which reported that the effect of insulin and ABA on body weight (BW) is opposite, as insulin induces an increase while ABA favoring a decrease. Insulin inhibits AMPK and the metabolic responses to low cell energy levels via protein kinase B.[22]

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Our results showed that diabetic rats displayed myocardial hypertrophy as supported by the significant increase in HW/BW ratio. These findings were in harmony witha former studywhich reported thatan increase in the HW may be related to an increase of water content, inflammatory cells infiltrations, oxidative stress, and increased uptake of glucose in the myocardium.[28] Myocardial hypertrophy could also be explained by increasing fatty acid oxidation in diabetics, leading to lipid accumulation in the myocardium. We have demonstrated that treatment of diabetic rats with ABA significantly decreased the HW/BW attenuating cardiac hypertrophy. This finding was in agreement with a study in 2019which observed that treatment of type II DM with ABA exerted positive effects on blood glucose, insulin, and HOMA-IR that reflected on HW/BW ratio.[29]

In the present study, it was found that cardiac enzymes (Cardiac troponin I, CK-MB, and LDH) in untreated diabetic rats were significantly elevated in comparison to the normal control group.This result is consistent with a study performed in 2012.[30]Also, we found that cardiac enzymes were significantly reduced in diabetic rats treated with ABA and or glibenclamide in comparison to untreated diabetic one, this means that long term treatment with ABA may help in reducing cardiac damage that occurs in diabetic cardiomyopathy it's maybe due to the anti-apoptotic effect of ABA. It has been documented that ABA can induce the expression of antioxidant genes and enhance the capacity of antioxidant defense systems in plants.[31]Furthermore, it has been reported that ABA reduces brain oxidative stress in rats. [32]Also, the study showed that the combined treatment group resulted in more cardioprotection by more decrease in cardiac troponin I, LDH, and CK-MB than single treatment with either glibenclamide or ABA. In line with these data, a previous study observed that ABA administration, resulting in GLP-1 release, produced both glycemic control and protective effects on the cardiovascular system.[33] A previous study reported that ABA administration improved atherosclerosis in ApoE-/- mice. [34]

Oxidative stress is considered the underlying mechanism for diabetes and its complications.[35]When the free radicals accumulate and cannot be removed by antioxidant enzymes;the accumulated free radicals promote lipid peroxidation, which induces cell damage. The main product of lipid peroxidation is Malondialdehyde (MDA), therefore, the tissue content of MDA reflect the degree of lipid peroxidation. [36]

In our study, there was a significant increase in the cardiac level of MDA and a significant decrease in the cardiac level of CAT in the untreated diabetic group as compared to the normal control group. This result is consistent with several studies that reported increased levels of lipid peroxides in the myocardium of diabetic rats.[37]

On the other hand, the administration of ABA increased the myocardial content of catalase and reduced the level of MDA. Therefore, the results of the present study suggest that ABA can reduce the toxicity of the heart by ROS scavenging ability and improving the antioxidant capacity. This result was in agreement with a recent study which concluded that the

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administration of ABA contributes to improving heart function via modulation of NO synthesis.[38]

Regarding the electrophysiological properties, the untreated diabetic group showed prolonged QTc interval as compared to the normal control group, this result is consistent with a previous study in 2015.[39] The possible mechanism was the decrease of expression ATP- sensitive potassium (KATP) channels, as evidenced in both diabetic rats and high glucose-treated cardiomyocytes, which increased the susceptibility to arrhythmia**.** [40]

Administration of ABA significantly restores the ECG pattern near to normal, indicating its protective effects on the cell membrane and electrical discharges, which may be due to its antioxidant property that maintained the integrity and permeability of cellular membranes. The intercellular connexin-43 (Cx43) channels are essential for direct connection between cardiomyocytes, ensuring action potential and signal propagation resulting in synchronization of heart function**.**[41] Previous study reported that myocardial Cx43 mRNA levels were lesser in diabetic versus non-diabetic rats and were enhanced by ABA supplementation**.**[29] This deterioration of Cx43 levels may be behind the prolongation of the QTc thereby affecting heart function in DM.

Finally, regarding pathological examination of the heart, untreated diabetic rats showed; degenerative changes of myocardial muscle with marked inflammation marked congestion of blood vessels, and marked fibrosis. These changes were similar toa previousstudythatfound an increase of collagenandα-SMA expression in the heart of diabetic rats.[42] This cardiac alteration could be related to hyperglycemia, hypoinsulinemia, and impaired lipid metabolism together with intracellular oxidative stress which leads to inflammatory infiltration followed by DNA damage and apoptosis**.**[43]However, supplementation of diabetic rats with ABA and/or glibenclamide has been shown to improve DCM and cardiac architecture. So, abscisic acid was able to protect the heart against diabetes-induced cellular injury through its ability to reduce hyperglycemia-induced inflammation and apoptosis together with improving connexin-43 expression and its antioxidant effect.

**Conclusion**

ABA reduceddiabetic cardiomyopathy through its anti-oxidant, anti-fibrotic, hypoglycemic, anti-inflammatory effects, and modulation of NO release. Therefore, ABA may be beneficial for the management of type II diabetes mellitus in combination with anti-diabetic drugs.

## References

**1- Abdul-Ghani M, Jayyousi A, De-Fronzo R, Asaad N and Al-Suwaidi J.** Insulin resistance the link between type II DM and CVD: Basic mechanisms and clinical implications. *CurrVascPharmacol.* 2019; 17 (2):153- 63.

ISSN:0975-3583,0976-2833 VOL12,ISSUE04,2021

**2- Ni R,Zheng D, Xiong S, Hill D, Sun T, et al.** Mitochondrial calpain-1 disrupts ATP synthase and induces superoxide generation in type-1 diabetic hearts: a novel mechanism contributing to diabetic cardiomyopathy. *Diabetes.*2015; 65(1):255-68

**3- Van Heerebeek L, Hamdani N, Handoko M, Falcao-Pires I, Musters R, et al.** Diastolic stiffness of the failing diabetic heart: importance of fibrosis, advanced glycation end products, and myocyte resting tension. *Circulation.* 2008; 117(1): 43-51.

**4- Do Lee C,Folsom A, Pankow J and Brancati F.** cardiovascular events in diabetic and non-diabetic adults with or without history of myocardial infarction. *Circulation*. 2004; 109(7):855- 60.

**5- Soufy H,Lin T, Das S and Zakaria Z.** Histological changes in the heart and the proximal aorta in experimental diabetic rats fed with Piper sarmentsoum. *African Journal of Traditional, Complementary and Alternative Medicines.* 2012; 9(3): 396-404.

**6- Fonarow G. and Srikanthan p.** Diabetic cardiomyopathy. *Endocrinology and metabolism clinics of North America.*2006; 35(3): 575-99.

**7- Malara A, Fresia C, Di Buduo C, Soprano P, Moccia F, et al.** The plant hormone abscisic acid is a prosurvival factor in human and murine megakaryocytes. *J Biol Chem*. 2017; 292(8):3239–51.

**8- Bruzzone S, Ameri P, Briatore L, Mannino E, Basile G, et al.** The plant hormone abscisic acid increases in human plasma after hyperglycemia and stimulates glucose consumption by adipocytes and myoblasts. *FASEB J.* 2012; 26: 1251–60.

**9- Bruzzone S, Magnone M, Mannino E, Sociali1 G, Sturla L, Fresia C, et al. A**bscisic acid stimulates glucagon-like peptide-1 secretion from L-cells and its oral administration increases plasma glucagon-like peptide-1 levels in rats. *Plos One J.*2015; 10(10): 0140588.

**10- Bassaganya-Riera J, Guri A, Lu P, Climent M, Carbo A, Sobral B, et al.** Abscisic acid regulates inflammation via ligand binding domain-independent activation of peroxisome proliferator-activated receptor γ. *J Biol Chem*. 2011; 286(4):2504–16.

**11- Lu P, Hontecillas R, Philipson C and Bassaganya-Riera J.**Lanthioninesynthetase component C-like protein 2: a new drug target for inflammatory diseases and diabetes. *Curr Drug Targets.*2014; 15:565–72.

**12- Vigliarolo T , Guida L , Magnone M, Ameri P, Lazzarini E, Fresia C, et al.** Abscisic acid: a new player in cardiomyocyte protection from ischaemia? Cardiovasc Res SupplCardiovascBiolPrevCardiol Testing, *Poster Sess.* 2016; 111 (S1):11–3.

**13- Badole S, Bagul P, Mahamuni S, Khose R, Joshi A, Jangam G, Ghule A, Raut C, KhedkarVandCoutinho E.** Oral L-glutamine increases active GLP-1 (7–36) amide secretion

ISSN:0975-3583,0976-2833 VOL12,ISSUE04,2021

and improves glycemic control in streptozotocin–nicotinamide induced diabetic rats, *Chem. Biol. Interact.*2013; 203: 530–41.

**14-Erejuwa O, Sulaiman M, Wahab K, Sirajudeen M, Salleh M and Gurtu S.** Glibenclamide or metformin combined with honey improves glycemic control in streptozotocin-induced diabetic rats. *Int J Biol Sci.*2011; 7(2): 244-52.

**15-Sheth D,Shah K, Chavda J and Desai T.** Effect of abscisic acid on dyslipidemia in fructose-induced insulin-resistant rats.*International Journal of Universal Pharmacy and Life Sciences.* 2012; 2(1): 140- 46.

**16-Chevenne D, Ruiz J, Lohmann L**, **Laudat A, Leblanc H, et al.** Immunoradiometric assay of human intact proinsulin applied to patients with type II diabetes, impaired glucose tolerance, and hyperandrogenism. *Clin Chem*. 1994; 40(5):754–7.

**17-Matthews D, Hosker J, Rudenski A, Naylor B, Treacher D, et al.** Homeostasis model assessment: insulin resistance and b-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia.*1985; 412–19.

**18- NehaKand LubnaA.** Evaluation of cardio protective effect of tinospora cordifolia against isoprenaline induced myocardial infarction in rats. *Int. J. Curr. Microbiol. App. Sci.***(2014);** 3(3): 543-55.

**19- Masiello P, Broca C, Gross R, Roye M, Manteghetti M, et al.** Experimental NIDDM: development of a new model in adult rats administered streptozotocin and nicotinamide. Diabetes.1998; 47: 224–9.

**20- Wallace T, Levy J, and Matthews D.** Use and abuse of HOMA modeling. *Diabetes Care.2004;* 27(6):1487-95.

**21- Nath S, Ghosh S and Choudhury Y.** A murine model of type II diabetes mellitus developed using a combination of high-fat diet and multiple low doses of streptozotocin treatment mimics the metabolic characteristics of type II diabetes mellitus in humans. *Journal of Pharmacological and Toxicological Methods*.2017; 84:20-30.

**22- Magnone M, Sturla L, Guida L, Spinelli S, Begani G, et al.** Abscisic Acid: A Conserved hormone in plants and humans and a promising aid to combat prediabetes and the metabolic syndrome.*Nutrients*. 2020; 12(6): 1724.

**23- Booz V, Christiansen C, Kuhre R, Saltiel M, Sociali G, et al.** Abscisic acid stimulates the release of insulin and GLP-1 in the rat perfused pancreas and intestine. *Diabetes Metab. Res. Rev*. 2019; 35(2):3102.

ISSN:0975-3583,0976-2833 VOL12,ISSUE04,2021

**24- Magnone M, Leoncini G, Vigliarolo T, Emionite L, Sturla L, et al**. Chronic intake of micrograms of abscisic acid improves glycemia and lipidemia in a human study and high-glucose fed mice. *Nutrients.* 2018; 10(10): 1495.

**25- Reyes B, Bautista A,Tanquilut N, Anunciado R, Leung A, et al.** Anti-diabetic potentials of Momordicacharantia and Andrographispaniculata and their effects on estrous cyclicity of alloxan-induced diabetic rats. J Ethanopharmacol.2006; 105: 196-200.

**26- Yang S, Wang S, Yang B, Zheng J, Cai Y, et al.** Weight loss before a diagnosis of type 2 diabetes mellitus is a risk factor for diabetes complications. Medicine. 2016; 95(49): 5618.

**27- Sturla L, Mannino E, Scarfì S, Bruzzone S, Magnone M, et al.** Abscisic acid enhances glucose disposal and induces brown fat activity in adipocytes in vitro and in vivo. *Biochim.Biophys.* 2017; 1862: 131–44.

**28- Fang W,Wang C, He Y, Zhou Y, Peng X, et al.** Resveratrol alleviates diabetic cardiomyopathy in rats by improving mitochondrial function through PGC-1alpha deacetylation. *ActaPharmacol Sin*. 2018; 39(1): 59-73.

**29- Mostafa A, Samir S and Mahdi M.** Effect of abscisic acid on the diabetic changes in rat myocardium. *Bull. Egypt. Soc. Physiol. Sci.*2019; 39(1):1-16

**30- Yu W, Wu j, Cai F, Xiang J, Zha W, et al.**Curcumin alleviates diabetic cardiomyopathy in experimental diabetic rats. *PLoS One J*. 2012; 7(12):52013.

**31- Sakthivel P, Sharma N, Klahn P, Gereke M and Bruder D**. Abscisic Acid: A phytohormone and mammalian cytokine as novel pharmacon with potential for future development into clinical applications. *Current medicinal chemistry.* 2016; 23(15):1549-70.

**32- Wang M, Oppedijk B, Lu X, Van Duijn B and Schilperoort R.** Apoptosis in barley aleurone during germination and its inhibition by abscisic acid. *Plant molecular biology.*1996; 32(6):1125-34.

**33- Ezcurra M, Reimann F, Gribble F and Emery E.** Molecular mechanisms of incretin hormone secretion. *CurrOpinPharmacol*.2013; 13: 922–7.

**34- Guri A, Misyak S, Hontecillas R, Hasty A, Liu D, et al.** Abscisic acid ameliorates atherosclerosis by suppressing macrophage and $CD^{4+}$ T cell recruitment into the aortic wall. *J Nutr Biochem*.2010; 21: 1178–85.

**35- Tokatli A, Yiginer O, and Kilicaslan F**. Effect of oxidative stress on ventricular repolarization in patients with type II diabetes: non-invasive quantification via transmural dispersion of repolarization. *Endocrine*.2016; 52(3)670-1.

ISSN:0975-3583,0976-2833 VOL12,ISSUE04,2021

**36- Wojtunik-Kulesza K, Oniszczuk A, Oniszczuk T and Waksmundzka-Hajnos M.**The influence of common free radicals and antioxidants on development of Alzheimer's disease.*Biomed Pharmacother*.2016; 78:39–49.

**37- Yang R, Jia Q, Liu X, Gao Q, Wang L, et al.** Effect of hydrogen sulfide on oxidative stress and endoplasmic reticulum stress in diabetic cardiomyopathy. *Chinese Journal of applied physiology*. 2016; 32(1):8-12.

**38- Elhadidy M, Elalfy M and Ali L.** Effect of Abscisic Acid on Isoproterenol-Induced Myocardial Infarction in Rats: A Possible Role of Nitric Oxide. Bull. Egypt. Soc. Physiol. Sci.2019; 40(2):16-30.

**39- Tiwari S and Ndisang J.**Upregulatingheme oxygenase improves electrocardiographic and hemodynamic parameters by potentiating insulin signaling in an obese model of diabetic cardiomyopathy. *Canadian Journal of Diabetes. 2015;*6(39): 538.

**40- Chen Z, Cheng Y, Chen L, Cheng K, Li Y, et al.** Increase of ATP-sensitive potassium (K ATP) channels in the heart of type I diabetic rats. *Cardiovascular diabetology*.2012; 11(8): 2840.

**41- Radosinska J, Kurahara L, Hiraishi K, Viczenczova C, Egan Benova T, et al.** Modulation of cardiac connexin-43 by omega-3 fatty acid ethyl-ester supplementation demonstrated in spontaneously diabetic rats. *Physiol Res.* 2015; 64(6):795-806.

**42- Attiaa H and Taha M.** Protective effect of captopril on cardiac fibrosis in diabetic albino rats: a histological and immunohistochemical study.*Benha Medical Journal.*2018;35:378– 85.

**43- Pan J, Guleria R, Zhu S, and Baker K.** Molecular mechanisms of retinoid receptors in diabetes-induced cardiac remodeling. *Journal of clinical medicine.*2014; 3(2):566-94.