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Article · May 2017

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Volume – 3; Issue - 2; Year – 2017; Page: 1094 – 1102
DOI: 10.22192/iajmr.2017.3.2.6

Indo – Asian Journal of Multidisciplinary Research (IAJMR)
ISSN: 2454-1370

REGENERATION OF B - CELLS IN ISLET LANGERHANS OF DIABETIC PANCREAS OF FEMALE RABBITS BY PHYTOESTEROL EXTRACT OF *Ceratonia siliqua* FRUIT

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Abstract

The present study was conducted in Collage of Veterinary Medicine, University of Basrah, to evaluate the effect of phytoesterol extract of *Ceratonia siliqua* fruit on biochemical parameters and histological examination by using pregnant diabetic female rabbits induced by alloxan. The study done was applied on 32 adult female rabbits, their weight ranged between (1500 – 2000 g) and aged between 7 - 7.5 M. The female mated with healthy male before 1st week of treated. The pregnant diabetic female rabbits divided randomly into three groups, each group consist of eight rabbits as the following. **Group 1:** Healthy female rabbits at 1st week of pregnant (-ve controls) administrated 3 ml of normal saline for 21 days. **Group 2:** Female rabbits at 1st week of pregnant given alloxan 150 mg\kg B.W. I.P for three days (+ve control) and remain for 21 days. **Group 3:** Female rabbits at 1st week of pregnant initially given alloxan150 mg\kg B.W. I.P. for three days, then treated with Insulin for 21 days. **Group 4:** Female rabbits at 1st week of pregnant initially given alloxan 150 mg\kg I.P. for three days, then treated with phytoesterol of *Ceratonia siliqua* fruit 1 ml\kg B.W. orally administration for 21 days. At the end of treatment period blood samples (10 ml) collected from animals heart. Blood sample put in plane tubes then centrifuge for obtained on serum for measurement biochemical parameters. Phytoesterol extract of whole fruit powder of *Ceratonia siliqua* in dose 1 ml/kg B.W. lowered glucose concentration 365 mg/dl to 129 mg/dl after 21days treatment in alloxan local rabbits, confirming antihyperglycemia effect of this plant animal and human. Histological observations with phytoesterol extract showed different phase of recovery of β - cells of the islet of langerhans of pancreas, which untreated diabetic rabbits were less in number and showed degree of atrophy. The most important finding of the present study was observation of the presence of small scattered islet among the acinartissue in some experimental animal, which may reflect neoformation of islet from pre-exsist ingislet cells. The liver of alloxan diabetic rabbits showed hydropic degeneration, fatty change and necrosis at some place but liver of animal treated with phytoesterol extract was normal. The kidney of alloxandiabetic rabbits revealed dilatation of inner cortical tubules and minimal partial capsular fibrosis, vacuolation of sub-capsular cortical tubules, infiltrations of inflammatory cells, vascular congestion and narrowed Bowman's space, glomeruli with high cellularity, cystic renal cortical tubules but kidneys of diabetic rabbits treated with phytoesterol extract of *Ceratonia siliqua* showed normal architecture. In addition to the kidneys of rabbits treated with Phytoesterol extract of *Ceratonia siliqua* fruit revealed amelioration in the kidneys compared to group of diabetic by alloxan alone. It is concluded that good anti-diabetic activity, hypoglycemia effect, amelioration of histological examination corroborating the folk use of phytoesterol extract of *Ceratonia siliqua* fruit preparations, and contributing for its pharmacological validation.

Key words: *Ceratonia siliqua*, Insulin, Alloxan, Biochemical Parameters, Histological Examination, Diabetes Mellitus and Rabbits.

1. Introduction

Diabetes mellitus is chronic disease and still one of the most important causes of death. According to the report by World Health Organization (WHO, 2015), 9 % of adults in the world suffer from diabetes and this disease will be the 7th leading cause of death in 2030 (Wild *et al*., 2004). The occurrence of diabetes during pregnancy may be classified into clinical diabetes, in cases previously diagnosed with type 1 or type 2 diabetes, which were previously known as insulin- and non-insulin dependent diabetes, respectively. T_1D results from pancreatic β-cell degeneration and was characterized by lack of insulin production, while patients with T_2D show a state of insulin resistance and usually relative insulin deficiency. Over time, diabetic patients with poor management undergo micro- and macro-vascular complications including nephropathy, retinopathy, neuropathy and cardiovascular diseases and gestational diabetes (Vambergue and Fajardy, 2011).

In pregnancies complicated by diabetes, hyperglycemia were altered and associated with both maternal and fetal complications causing reproductive abnormalities that enhance spontaneous abortion, congenital anomalies, and neonatal morbidity and mortality (Merzouk *et al*., 2000; Metzger, 2002; Eriksson, 2008; Vambergue and Fajardy, 2011). Oxidative stress has been implicated as a contributor to both the onset and the progression of diabetes and its associated complications. Some of the consequences of an oxidative environment are the development of insulin resistance, β-cell dysfunction, impaired glucose tolerance, and mitochondrial dysfunction, which can lead ultimately to the diabetic disease state. Experimental and clinical data suggest an inverse association between insulin sensitivity and reactive species oxygen (ROS) levels (Hamada *et al*., 2009). Maternal diabetes is a predisposing factor for embryonic lethality, congenital abnormalities and placental defects (Merzouk *et al*., 2000; Metzger, 2002; Eriksson, 2008).

Ceratonia siliqua common name carob is native to Mediterranean regions and is found in south of Syria, India and most of Mediterranean areas as well as in California. The unripe pod is green, moist and very astringent, but the ripe pod is sweet. The broken pod has a characteristic odor caused by its 1.3 % isobutyric acid content (Marakis, 1996). The main application of carob pods in animal feed production, but in some area, carob seeds is used like tea and coffee (Kumazawa *et al*., 2002; Batlle and Tous, 1997). Carob powder is a natural sweetener with flour and appearance similar to chocolate; therefore it is often used as cocoa substitute. Carob germ flour is used as dietic human food (Ayaz *et al*., 2007) or as a potential ingredient in cereal - derived foods for celiac people (Inoue *et al*., 1994). *Ceratonia* pulp is prepared for treatment of mouth inflammation (Nidal *et al*., 2005). Similarly, *Ceratonia siliqua* seed was useful to treat and improve diabetes symptoms because it has compounds such as fibers, phytosterols and tocopherol (Jim, 2005). The present study was aimed to investigate the hypoglycemic effect of phytoestrol extract of *Ceratonia siliqua* fruit by using an experimental animal model of Alloxan - induced damage of β-cell of langerhans islet in pregnant rabbits. To determine its effect on histological examination in diabetic pregnant rabbits and it could ameliorate the diabetes mellitus and comparison of effects of phytosterol extract with insulin.

2. Materials and Methods

Drugs and Chemicals

Alloxan obtained from Safa co. Diala - Iraq, and insulin provided from Glaxo Smith Kline, S.A. Aranda de Duero.

Plant Material

Phytoesterol had been extracted from carob fruits (*Ceratonia siliqua*) that were used in this study. The carob was hand - picked from

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Received: 28.01.2017; *Revised*: 24.02.2017; *Accepted*: 15.03.2017.

IAJMR ISSN: 2454-1370

local market. It was washed with tap water. The fruits of the carob were turned to powder with the help of an electric grinder and kept in dark container at 25 °C.

Preparation phytoester oil extract from carob fruits (*Ceratonia siliqua*)

Fifty grams of dried carob fruits powder was defatted with (500 ml) of n-hexane for 6 hrs by soxhlet. The combined n-hexane extract was concentrated below 50 °C under reduced pressure in a rotary evaporator to get 7 ml of brown oily (Harborn, 1993).

Experimental Animals

Thirty two adult female rabbits weight ranged between (1500 – 2000 mg) kept for an adaptation period for 1 month in the animal house of Veterinary Medicine College / Basrah University. The experimental animals were kept in individual cages, provided with standardration in addition to green alfalfa (*Medicago sativa*) and tap water *ad libitum* and given a prophylaxis drug against coccidiosis (Amprollium 1 g/L of drinking water).

Experimental design

The rabbit divided into four groups of comprising 8 animals in each group as the following: **Group 1:** Healthy female rabbits at 1st week of pregnant (-ve control) administrated 3 ml of normal saline for 21days. **Group 2:** Female rabbits at 1st week of pregnant initially given alloxan 150 mg\kg B.W dissolved in 3 ml of normal saline by I.P for three days (+ve control) and remain for 21 days. **Group 3:** Female rabbits at 1st week of pregnant initially given alloxan150 mg\kg B.W dissolved in 3 ml of normal saline by I.P. for three days and then treated with Insulin for 21 days. **Group 4:** Female rabbits at 1st week of pregnant initially given Alloxan 150 mg\kg B.W dissolved in 3ml of normal saline by I.P. for three days and then treated with phytoesteriol extract of *Ceratonia siliqua* fruits 1 ml\kg B.W for 21days.

Induction of Diabetes Mellitus

Diabetes mellitus were induced in twenty four starved pregnant female rabbits by giving alloxan injected by one ml size syringe and in dose 150 mg\kg for three days.

Collection of Blood Samples

Blood samples (10ml) were collected from each animals at end of experiment by the heart (cardiac puncture). The blood was deposited into tube without anticoagulant and then the blood samples were centrifuged at 3000 rpm for 15 minutes and serum samples stored in polyethylene eppendorff tubes at -20 ºC, which then used to study the biochemical parameters (Serum glucose).

Study parameter

Serum Glucose Measurement

Serum glucose was enzymatically measured by using a linear chemical kit (RANDOX\ GLUC - PAP, United Kingdom) (Barham and Trinder, 1972; Teuscher and Richterich, 1971).

Histological Techniques

The animals were sacrificed at the end of the experiment and the organ samples were taken as pancreas, liver, kidneys and ovaries. These organs were fixed in 10 % buffered formalin, dehydrated progressively in increased ethanol concentrations, treated with xylene and embedded in paraffin. Five microns thickness sections of paraffin - embedded tissue were mounted on glass slides and stained with Haematoxyline and Eosin stain (H & E stain) (Bancroft *et al*., 1990; Luna, 1993).

Statistical Analysis

The results of the present study were analyzed by using two - way covariance (ANOVA) test in all study. All statistical calculations were carried out by the aid of the statistical package SPSS V. 17 (SPSS Inc.). The data were expressed as means ± standard deviation (X ± SD). Least significant different test (LSD) was calculated to test difference between means of groups and sub-groups (Stat Soft Inc, 2009).

3. Result

Effect of Phytoestrol Extract of *Ceratonia siliqua* Fruit and Insulin on Glucose Level in serum of Pregnant Diabetic Female Rabbits Induced by Alloxan

The obtained results in Table - 1 revealed significant increase (P≤0.05) in glucose concentration in serum of diabetic female rabbits induced by alloxan group compared to control and another treated groups while the results showed no significant change (P≤0.05) glucose concentration in serum of diabetic female rabbits treated with phytoesterol of *Ceratonia siliqua* fruit compared to control group and insulin group.

Table – 1: Effect of Phytoestrol Extract of *Ceratonia siliqua* Fruit and Insulin on Glucose Level in Serum of Pregnant Diabetic Female Rabbits Induced by Alloxan (Mean ± SD) (n = 8)

Parameters / *Treatments*	*Glucose mg/dl*
Control (Normal Saline)	*111.62±7.53 B*
Alloxan (150mg/kg)	*356.38±71.19 A*
Alloxan + Insulin	*107.58±36.77 B*
Alloxan + Phytoestrol (1 ml/kg)	*129.60±20.31 B*

N = Number of animals, Capital letters denote differences between groups, P≤0.05 vs Control, NS = Non - significant.

Histological Examination

Histological observation with phytoesterol extract showed different phase of recovery of β-cells of the islet of langerhans of pancreas, which untreated diabetic rabbits were less in number and showed degree of atrophy. The most important finding of the present study was observation of the presence of small scattered islet among the acinar tissue in some experimental animal, which may reflect neoformation of islet from pre-exsisting islet cells. The liver of alloxan diabetic rabbits showed hydropic degeneration, fatty change and necrosis at some place but liver of animal treated with phytoesterol extract was normal. The kidney of alloxandiabetic rabbits revealed dilatation of inner cortical tubules and minimal partial capsular fibrosis, vacuolation of sub-capsular cortical tubules, infiltrations of inflammatory cells, vascular congestion and narrowed Bowman's space, glomeruli with high cellularity, cystic renal cortical tubules but kidneys of diabetic rabbits treated with phytoesterol extract of *Ceratonia siliqua* showed normal architecture. In addition to the kidneys of rabbits treated with Phytoesterol extract of *Ceratonia siliqua* fruit revealed amelioration in the kidneys compared to group of diabetic by alloxan alone.

Pancreas

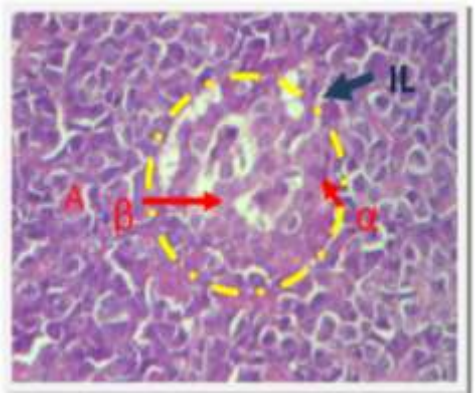

Figure - 1: Section of Pancreas of rabbits (-ve control group) showing present normal islet of langerhans (IL) cells granulated cytoplasm of islet cell with light and large nuclei (β-cell) or with small, dark nuclei on periphery (α-cell) and normal acini (A), stained with H & E (400 X)

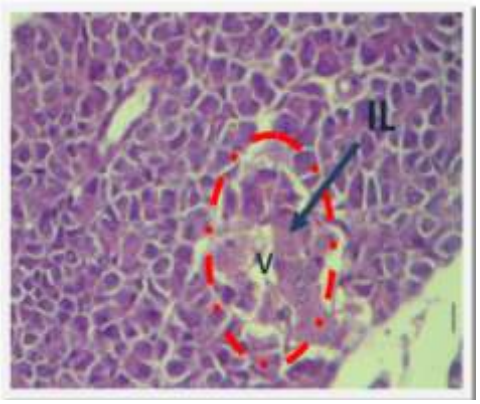

Figure - 2: Section of Pancreas of diabetic rabbits (+ve control group) showing hypertrophy and hyperplasia of β-cells of islets of langerhans associated with pyknosis of their nuclei, degenerate vacuolated islet of langerhans (IL), stained with H & E (400 X)

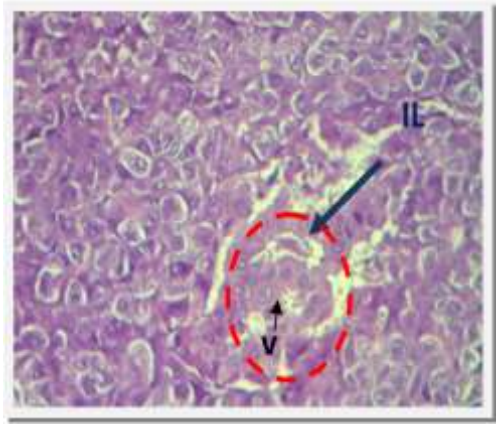

Figure - 3: Section of Pancreas of diabetic rabbits treated with insulin showing islet of langerhans (IL) with vacuolated cells (V), hyperplasia of β-cells of islets of langerhans associated with pyknosis of their nuclei Stained with H & E (400 X)

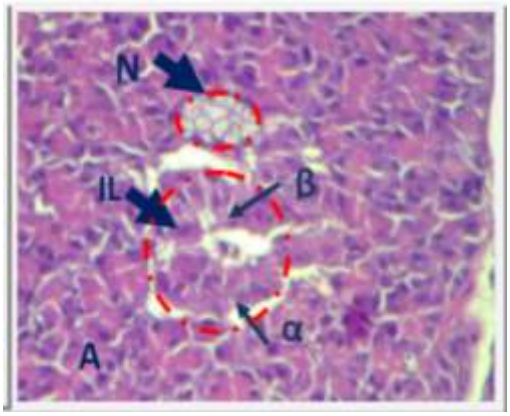

Figure - 4: Section of Pancreas of diabetic rabbits treated with Phytoesterol of *Ceratonia siliquia* showing regeneration proliferation of islet of langerhans (IL), varying size of islet with large cell, showing small islet (IL) appear as newly formed cells (N), normal acini (A), stained with H & E (400 X)

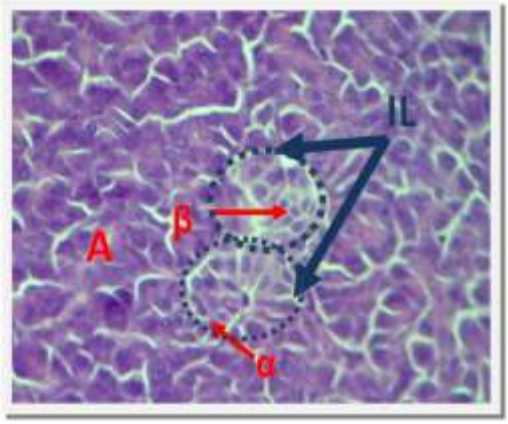

Figure - 5: Section of Pancreas of diabetic rabbits treated with Phytoesterol of *Ceratonia siliquia* showing small islet appear as newly formed cells and normal acini (A), stained with H & E (400 X)

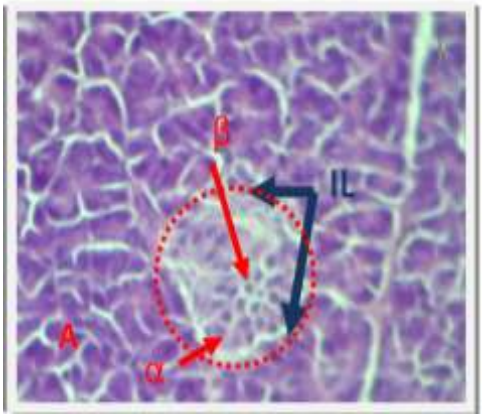

Figure - 6: Section of Pancreas of diabetic rabbits treated with Phytoesterol of *Ceratonia siliquia* showing normal small islet (IL) appear as newly formed cells granulated cytoplasm of islet cell with light and large nuclei (β - cell) or with small, dark nuclei on periphery (α-cell) and normal acini (A), Stained with H & E (400 X)

Liver

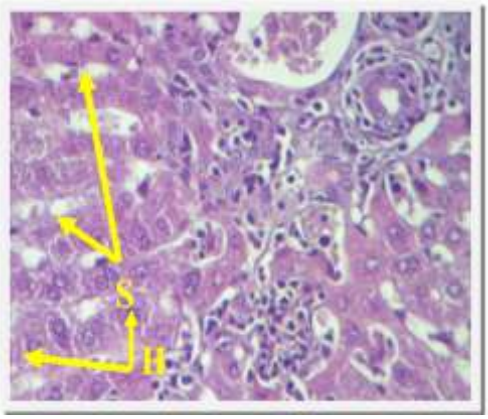

Figure - 7: Section of liver of female rabbit (-ve control group) showing per portal region with a few mononeuclear cells, Normal hepatocyte (H) and normal sinusoid(S), Stained with H & E (400 X)

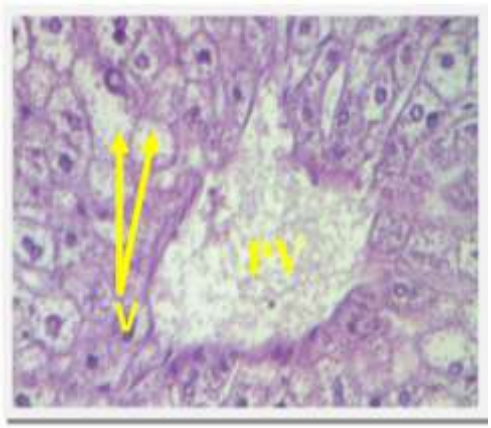

Figure - 8: Section of liver of diabetic female rabbit (+ve control group) showing minimal diffuse vacuolation (V) of hepatocytes, occasional foce of mononuclear cell, minimal periportal fibrosis, dilated portal vein, Bile duct proliferation, Stained with H & E (400 X)

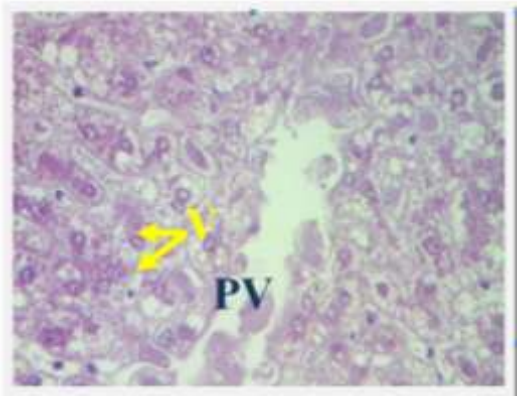

Figure - 9:-Section of liver of diabetic female rabbit treated with insulin showing minimal diffuse vacuolation (V) of hepatocytes, cystic dilatation of portal vein, minimal periportal fibrosis, dilated portal vein, Bile duct proliferation, stained with H & E (400 X)

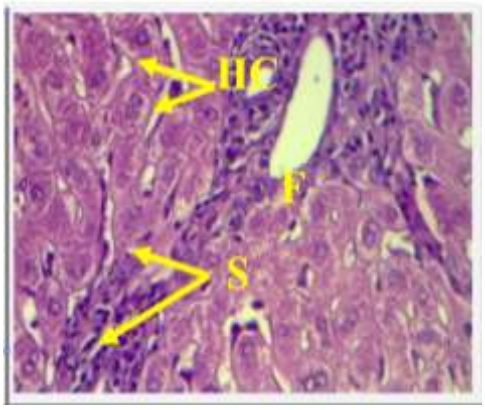

Figure - 10: Section of liver of diabetic female rabbit treated with Phytoesterol of *Ceratonia siliqua* showing per portal region of mononeuclear cells, Bile duct proliferation also in some part of septal fibrosis (F), Normal hepatocytes (HC) and normal sinusoid (S), stained with H & E (400 X)

Kidneys

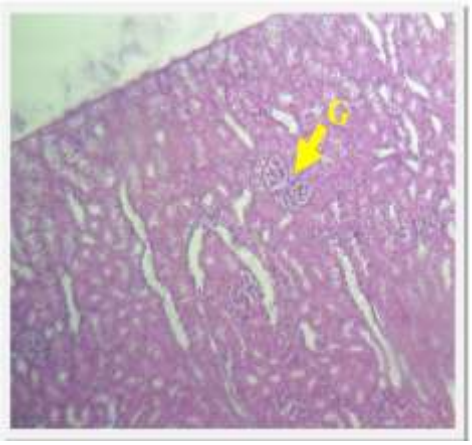

Figure - 11: Section of kidney rabbits (-ve control group) showing normal glomeruli (G), and normal epithelial cells lining of the renal tubules, stained with H & E. 100 X

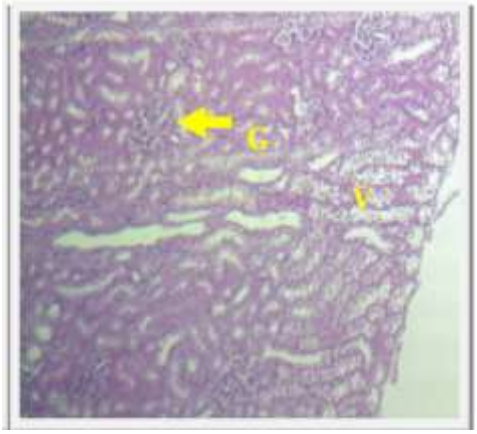

Figure - 12: Section of kidney diabetic rabbits (+ve control group) showing dilatation of inner cortical tubules and minimal partial capsular fibrosis (F), vacuolation of sub - capsular cortical tubules and atrophy of glomeruli (G), stained with H & E. 100 X

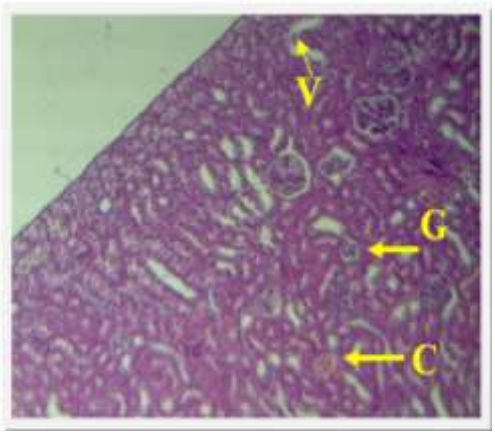

Figure - 13: Section of kidney diabetic rabbits treated with insulin showing dilatation of sub - capsular area with moderate vacuolation (V) of sub capsular cortical tubules, atrophy glomeruli (G) and vascular congestion(C), stained with H & E. 100 X

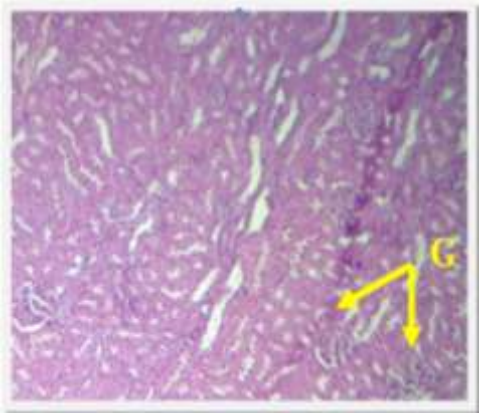

Figure – 14: Section of kidney diabetic rabbits treated with Phytoesterol of *Ceratonia siliqua* showing moderate vacuolation sub - capsular area of cortical tubules, also dilated tubules in inner cortex, stained with H & E. 100 X

4. Discussion

In alloxan diabetic rabbits, there was selective destruction of β-cells of islet of langerhans. The histopathological examination showed the reduced number of islet, degranulationof β-cells, hydropic degeneration, clumping of β-cells, pyknosis and necrosis. The necrosis was mostly found in the central larger islet because the center portion of the larger islet is the first to be affected by alloxan. The interesting aspect of the present study is the observation of newly formed islets. However there is already some indication of such change from the study of histological examination and measurement of glucose concentration. The pancrease of rabbits treated with phytoesterol extract of *Ceratonia siliqua* fruit showed amelioration of architecture of islets langerhan's compared to pancreas treated with alloxan alone. The pancreas of rabbits treated with phytoestrol extract showing nearly normal structure of Islets of Langerhans embedded within the exocrine portions which are formed of pyramidal cells with basal nuclei. After supplementation with phytoestrol extract the pancreas appeared similar to the control and most of the islets of Langerhans.

The protective effects of this plant on drug - induced β-cells destruction, increasing islets size, and β-cell population were presented. B-cell apoptosis and replication rates, islet size, and islet neogenesis are the major determinants of pancreatic endocrine capability for insulin secretion and glucose homostasis (Montanya and Tellez, 2009). Changing the balance of β-cell replication and apoptosis alters the length of β-cell cycle which contributes to the islet size and insulin release. Decreasing apoptosis results in the enhancement of β-cell viability and increase in insulin production. Intrinsic and extrinsic pathways are considered as two general routes for the activation of apoptosis. The former is activated by stress factors including growth factor deprivation, cell cycle disturbance, and DNA damage, which lead to mitochondrial release of cytochrome *c* and subsequent stimulation of caspase.

The oxidative stress plays an important role in β-cell dysfunction and apoptosis (Yang *et al*., 2011). Because of poor antioxidant capacity, beta cells are vulnerable to the oxidative stress induced by both T_1D insulitis and T_2D glucotoxicity (Sharma *et al*., 2009). Therefore, drugs and phytochemicals that improve glycemia and oxidative stress ameliorate or prevent islet lesions. In this regard, protective effect of some phytochemicals on pancreas has been found to be mediated through their antioxidant effects. Zhou *et al*. (2009) reported that treatment with berberine restored the reduced superoxide dismutase activity and increased lipid peroxidation of pancreas of diabetic animals to the near control level. These antioxidant effects of berberine, therefore, mediate its anti-apoptotic action against β-cell apoptosis in insulin-resistant animal models and against palmitate-induced lipoapoptosis in HIT-T15 insulin producing cells (Gao *et al*., 2011; Wu *et al*., 2011). Similarly, the β-cell protective effect of *N. sativa* can be attributed to the antioxidant properties of this plant, which increases superoxide dismutase activity, inhibites lipid peroxidation, and decreases the generation of reactive oxygen species (ROS) in pancreas tissue (Abdelmeguid *et al*., 2010). In addition to the direct evidence for pancreas, protective effects of the phytochemicals on other tissues may support their beneficial actions on pancreatic structure of diabetic rabbits.

5. Conclusion

Destruction of pancreatic islets is the major determinant for the onset of hyperglycemia and development of complications in insulin - dependent diabetic patients. Preventing β-cell degeneration, stimulating endogenous regeneration of islets will be of essential approaches for T_1D management. Therefore, development of phytochemical products with β-cell regenerative property can be a promising option for the patients who have lost their mass of functional islet cells. One of plants that have been investigated for diabetes, a small fraction has shown the regenerative property, which was described in this paper. For most of these herbs, however, the number of studies supporting their beneficial effects on pancreas is not enough. *Ceratonia siliqua* had more than one piece of evidence for their regenerative property so that their consumption may decrease insulin dependence on diabetic patients. The exact

mechanism responsible for the protective/ regenerative effects of phytochemicals on pancreatic islets is yet to be elucidated. However, antioxidant property of phytochemicals may in part mediate their protective action against pancreatic β-cell apoptosis. Regardless of the molecular mechanisms, it seems that patients at the earliest stages of diabetes can be treated with these plants to delay or prevent the full destruction of pancreatic islets. Also, construction of polyherbal compounds through the combination of these phytochemicals may yield more potent regenerative agents for beta cells.

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How to Cite this Article:

Faten S. Mounce and Muna A. AL-Saeed. 2017. Regeneration of B – cells in Islets Langerhans of Diabetic Pancreas of Female Rabbits by Phytoesterol Extract of *Ceratonia siliqua* Fruit. *Indo - Asian Journal of Multidisciplinary Research*, 3(2): 1094 – 1102.

DOI: 10.22192/iajmr.2017.3.2.6