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Research Article

Possible Protective Role of Parsley Extract on the Diabetic Pregnant Rats and Their Fetuses

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Abstract

Background and Objective: Gestational diabetes mellitus (GDM) is one form of diabetes. It causes obstetrical complications and affects between 5-18% of all pregnancies and leads to congenital malformations and long-term postnatal disorders. Supportive therapy in treatment of diabetes during pregnancy takes place by anti-diabetic plants such as parsley. The current study has been undertaken to investigate the possible anti-diabetic and antioxidant role of aqueous parsley extract on streptozotocin (STZ) induced gestational diabetes mellitus in rats. **Materials and Methods:** Fifty pregnant albino rats were categorized after mating into five groups: group C (control group), group D1 (pregnant rats injected with interperitoneally single dose of STZ (40 mg kg⁻¹ b.wt.) in the 1st day of gestation, group D1+P: Pregnant rats were treated with parsley extract (1 m/150 g b.wt.) from the 1st to the 19th day of gestation post injection with STZ (40 mg kg⁻¹ b.wt.), group D7: Pregnant rats were injected with STZ (40 mg kg⁻¹ b.wt.) on day 7 of gestation, group D7+P: Pregnant rats were treated with parsley extract (1 m/150 g b.wt.) from the 7th to the 19th day of gestation post injection with STZ (40 mg kg⁻¹ b.wt.). The pregnant rats were dissected on the 19th day of pregnancy and the uterine horns were removed freshly and then photographed. Abnormalities or any morphological changes were recorded, weight of fetuses and placenta and placental index were determined. Blood samples were collected to estimate the glucose and biochemical parameters of the main kidney functions. Also, kidney samples of fetuses were taken for the histopathological study. **Results:** Fetuses of the diabetic mothers showed some developmental changes such as very thin skin, very thin muscle layer under the skin, absence of eyelid and ear pinna, exencephaly and kyphosis. On the other hand, fetuses of the diabetic mothers which were treated with parsley leaves extract showed somewhat normal morphological development. According to the biochemical histopathological observations, the parsley leaf extract succeeded to minimize the drastic changes, which were observed in the diabetic rats and their fetuses. **Conclusion:** Administration of the parsley leaf extract has the ability to minimize the damage of hyperglycemia.

Key words: Gestational diabetes mellitus, pregnant rats, fetuses, parsley extract, kidney function

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Diabetes mellitus can damage numerous tissues especially the reproductive system^{1,2}. Diabetes mellitus is multifactorial disease and it has 3 types: type1: an autoimmune β -cell destruction, type 2: a combination of insulin resistance in the peripheral tissues and β -cell failure and the third type is gestational diabetes (GDM). Number of individuals affected by diabetes is expected to reach 438.4 million in 2030 all over the world³.

Gestational diabetes mellitus is a life-threatening disease characterized by hyperglycaemia as a result of failure in insulin production by pancreatic beta cells defects in insulin secretion, insulin action or both⁴. Diabetes during pregnancy leads to adverse short-term and long-term metabolic states in both the mother and fetuses^{5,6}.

GDM reduced the number of nerve fibers and thickness of the myelin sheath⁷. It is increasing year by year and affected by maternal age and obesity⁸. The insulin resistance (IR) is the common in the late stage of pregnancy in gestational diabetes mellitus⁹.

Mothers whom suffer from diabetes mellitus their infants have been at significantly greater risk for abortion, congenital malformations, stillbirth, perinatal morbidity and mortality. Fetuses of diabetic mothers have hypoinsulinemia that related to β -cell exhaustion showed growth retardation¹⁰.

Chemical drugs have side effects, so use of medicinal plants has a long history in treatment of lot of diseases and health maintenance¹¹. Medicinal plants are effective in controlling glucose level and they are considered as alternative therapy for treatment of diabetes mellitus¹². Parsley leaf is a source of natural antioxidants and have several functions in human body and prevent food from oxidation processes¹³. Flavonoids are one component of parsley and exhibit biological activities such as anti-inflammatory antiallergenic and antiviral¹⁴. Parsley is one of the richest sources of phenolic aglycone, apigenin which are common culinary herbs consumed globally¹⁵.

Parsley has wide range of pharmacological activities which are including brain protection, antioxidant, hepatoprotective, anti-diabetic, analgesic, laxative, spasmolytic, immunosuppressant, anti-platelet, gastroprotective, cytoprotective, estrogenic, diuretic, hypotensive, antibacterial and antifungal activities¹⁶.

Parsley extracts are used as antidiabetic and antioxidant agents in type 1 diabetes mellitus¹².

Kidney failure can lead to death in diabetes^{17,18}. Maternal hyperglycemia is associated with neonates that are at greater risk for future development of negative

health outcomes such as insulin resistance, obesity, metabolic syndrome and type 2 diabetes mellitus¹⁹.

Diabetes causes nephropathy, destroys distal tubular epithelium, cytoplasmic changes, thickness in small arteries and glomerulosclerosis which causes thickened glomerular basement membranes with increased extracellular matrix deposition^{20,21}.

Parsley maintains health of kidney and the histopathological examinations confirmed the potential prophylactic and curative roles of parsley aqueous extract in inhibition of formation of renal stones associated with decreased calcium kidney content^{22,23}. The current study aimed to investigate the possible anti-diabetic and antioxidant role of aqueous parsley extract.

MATERIALS AND METHODS

Experimental animals: A total of 50 female albino rats and 25 male, weight 200-220 g were selected. Rats fed on standard diet and some vegetables. Glucose level was determined (If the serum glucose level was more than 7.0 mmol L⁻¹, the rats were excluded). Before the experiment, all rats were stayed for 2 weeks in metal cages under standard laboratory conditions of light (12 h light/dark cycle), temperature 25 $\pm$ 5 and then the experiment was started.

Induction of pregnancy: Vaginal smears were collected daily for estrous cycle determination and then the estrous rats were placed with healthy male in the ratio of 2:1 for mating. In the following morning, mating was confirmed by presence of sperms in the vaginal smear and presence of the vaginal plug and that was considered as day zero of pregnancy²⁴. The pregnant rats were labeled and separated, after 1 week of mating, non-pregnant rats were excluded.

Generation of gestational diabetes mellitus: Diabetes was induced in rats by a single intraperitoneally injection of freshly prepared STZ solution (40 mg kg⁻¹ b.wt.) on day one of gestation²⁴. This dose was dissolved in citrate buffer (0.1 mol L⁻¹, pH = 4.5)²⁵. After 24 h of STZ injection blood glucose levels were checked using a glucometer (ACCUCHEK® Active Glucometer, Roche Diagnostics, Germany). If glucose levels ranged between 120-250 mg dL⁻¹, the rats were selected and used as gestational diabetes mellitus (GDM)²⁴.

Aqueous extract of parsley: The fresh parsley leaves were obtained from local market and carefully washed with tap water, chopped into small of pieces and left to dry in the dark at room temperature. They were stored in well-closed

cellophane. The air-dried leaves (100 g) were extracted by adding 1000 mL of boiled distilled water for 30 min. The extract was then filtered and the filtrates were given to pregnant rats 1 mL/150 g orally by stomach tube²⁶.

Experimental groups: About 50 pregnant Albino rats were used and categorized into five groups after mating: Group 1 (Control group C), group 2 (Pregnant rats were injected interperitoneally with a single dose of STZ (40 mg kg⁻¹ b.wt.) in the 1st day of gestation (D1), group 3: pregnant rats were treated with parsley extract (1m/150 g b.wt.) from the 1st to 19th day of gestation 1 h post injection with STZ (40 mg kg⁻¹ b.wt.) (D1+P), group 4: pregnant rats were injected with STZ (40 mg kg⁻¹ b.wt.) on day 7 of gestation (D7), group 5: Pregnant rats were treated with parsley extract (1 m/150 g b.wt.) from the 7-19th day of gestation one hour post injection with STZ (40 mg kg⁻¹ b.wt.) (D7+P). The pregnant females were dissected on the 19th day of pregnancy.

Morphological studies: On day 19 of gestation, pregnant rats were weighed, anesthetized with ether. The uterine horns were removed freshly and abnormalities or any morphological changes were recorded and weight of fetuses, placenta and placental index were determined.

Biochemical studies: After the pregnant rats were anesthetized by ether, blood was collected from the heart puncture by plastic syringes and left to coagulate and serum was separated by centrifugation at 3000 rpm for 15 min for the biochemical analysis serum glucose and main kidney function were determined.

Histopathological study: The samples of kidney of fetuses in all the treated and control groups were fixed in 10% neutral buffer formol and Carnoy's fluid for the histological study. The samples were washed and dehydrated in ascending grades of alcohol, cleared in xylene and embedded in paraffin wax. Sections (5 µ thick) were stained by hematoxylin and eosin²⁷ to evaluate the kidney damage and Mallory's trichrome stain for demonstrating collagen fibres²⁸.

Statistical analysis: Comparisons between groups were analyzed with one-way ANOVA using SPSS 19.0 statistical analysis software. Data were presented as Mean±SE. In all tests, $p \leq 0.05$ was considered statistically significant.

RESULTS

Morphological studies: Normal morphological characters of fetuses appeared clearly in the control group, which were isolated from the uteri of pregnant rats on the 19th day of gestation (Fig. 1a). Fetuses of the diabetic mothers showed a retarded fetuses with very thin skin, very thin muscle layer under the skin, absence of eyelid and ear pinna, exencephaly and kyphosis in group D1 and D7 (Fig. 1b, d). On the other hand, fetuses of the diabetic mothers which were treated with parsley leaves extract showed somewhat normal appearance in size and length of fetuses, normal eyelid, normal tail, but some fetuses showed elongated narrow head, subcutaneous hemorrhage and resorbed body in groups D1+P and D7+P (Fig. 1c, e). Table 1 showed that the fetal weights were significantly lower in groups D1 and D7 compared to the control group. Administration of parsley extract recorded no significant change in D7+P group compared to the control group, but still significant decrease was still detected in group D1+P. Placental weight and index were significantly increased ($p \leq 0.05$) in the diabetic groups (D1 and D7) and in D1+P group, but no significant changes were recorded in D7+P group.

Biochemical studies: A significant increase in fasting glucose level was observed in D1 and D7 groups (152.2 ± 22.18 , 140.6 ± 17.47) respectively compared to the control group (80.4 ± 12.50), but improvement in glucose level was realized in group D1+P and D7+P (101.8 ± 10.73 , 99.0 ± 16.82) respectively compared to the control group. The present results showed no significant change ($p \geq 0.05$) in the mean values of blood urea level in D1+P and D7+P groups (33.00 ± 4.63 and 30.60 ± 5.96 mg dL⁻¹) respectively, but there was a highly significant increase ($p \leq 0.01$) in D1 group (41.60 ± 2.31 mg dL⁻¹) and significant increase in D7 group (37.40 ± 4.09 mg dL⁻¹), compared to the control group

Table 1: Statistical analysis of fetal weight, placental weights and placental index in the different experimental groups

Parameters	Groups				
	C	D1	D1+P	D7	D7+P
Fetuses weight (g)	3.31 ± 0.15	$2.06 \pm 0.23^{**}$	$2.82 \pm 0.25^*$	$2.31 \pm 0.21^{**}$	3.04 ± 0.37
Placental weight (g)	0.59 ± 0.06	$0.75 \pm 0.11^*$	$0.74 \pm 0.14^*$	$0.78 \pm 0.53^*$	0.65 ± 0.13
Placental index (g)	0.18 ± 0.02	$0.41 \pm 0.81^*$	$0.29 \pm 0.09^*$	$0.34 \pm 0.54^*$	0.21 ± 0.68

Each value represented the mean ± standard deviation (SD). The values are considered significant at $*p \leq 0.05$ and highly significant at $**p \leq 0.01$ compared to the control group. C: Control, D1: Diabetic pregnant rats on day 1 of gestation, D1+P: Diabetic and parsley leave extract on day 1 of gestation, D7: Diabetic pregnant rats on day 7 of gestation, D7+P: Diabetic and parsley leave extract on day 7 of gestation

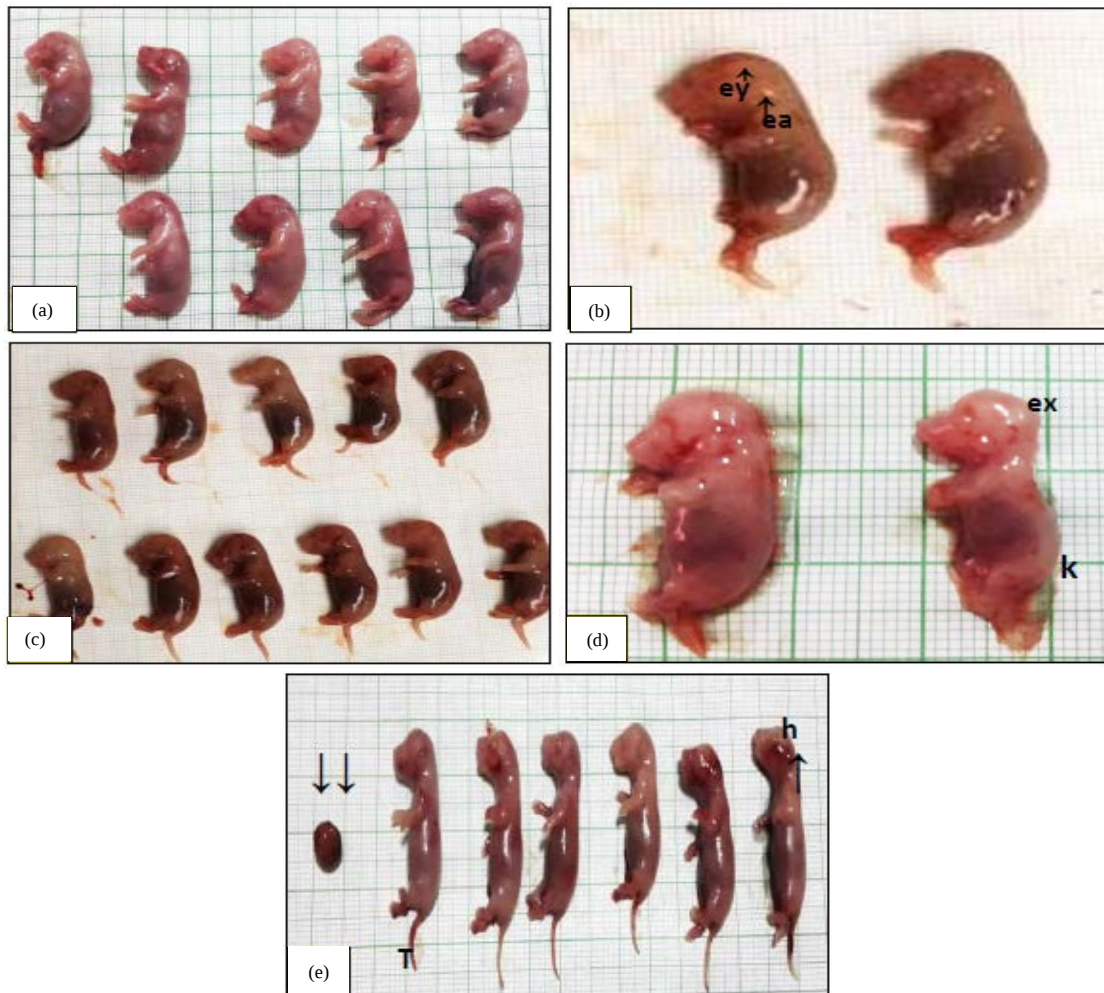


Fig. 1(a-e): Showing isolated fetuses on day 19 of gestation, (a) Normal morphological characters of fetuses of the control group, (b, d) Retarded fetuses with very thin skin, very thin muscle layer under the skin, absence of eyelid (ey) and ear pinna (ea), exencephaly (ex) and kyphosis (k) in groups D1 and D7, (c,e) showing slight improvement in size and length of fetuses, normal eyelid (ey), normal tail (T), but some fetuses show elongated narrow head, subcutaneous hemorrhage (h) and resorbed body (↓) in groups D1+P

(29.4 ± 5.07). There was no significant change ($p \geq 0.05$) in the mean values of the serum creatinine level in groups D1+P and D7+P, where the values reached 0.76 ± 0.04 and 0.86 ± 0.16 mg dL⁻¹, respectively. But it showed significant increase ($p \leq 0.05$) in groups D1 and D7 (1.03 ± 0.13 and 0.98 ± 0.17 mg dL⁻¹) respectively compared to the control group (0.77 ± 0.13 mg dL⁻¹).

Histopathological study of the fetal kidney: Histological pattern of the fetal kidney cortex of the control group showed normal architecture of the glomeruli, capsule and convoluted tubules (CTs) (Fig. 2a) with thin scattered collagen fibres (Fig. 3a).

Fetal kidney tissue of group D1 and D7 showed malformed, hypertrophied or congested glomeruli; atrophied and necrotic CT, numerous degenerated areas and lots of fibroblasts and external bleeding around the kidney (Fig. 2b, d). Reduced collagen fibres was detected in the cortex and medulla with brightly red stained glomeruli and hemorrhagic areas in fetal kidney cortex of group D1 (Fig. 3b), but increased collagen fibres with brightly red stained hemorrhagic areas were observed in group D7 (Fig. 3d).

Somewhat normal appearance of kidney tissue was demonstrated in fetal kidney tissue of groups D1+P and D7+P, but few hemorrhagic areas were still detected as shown in Fig. 2c, e, respectively with nearly normal content of collagen

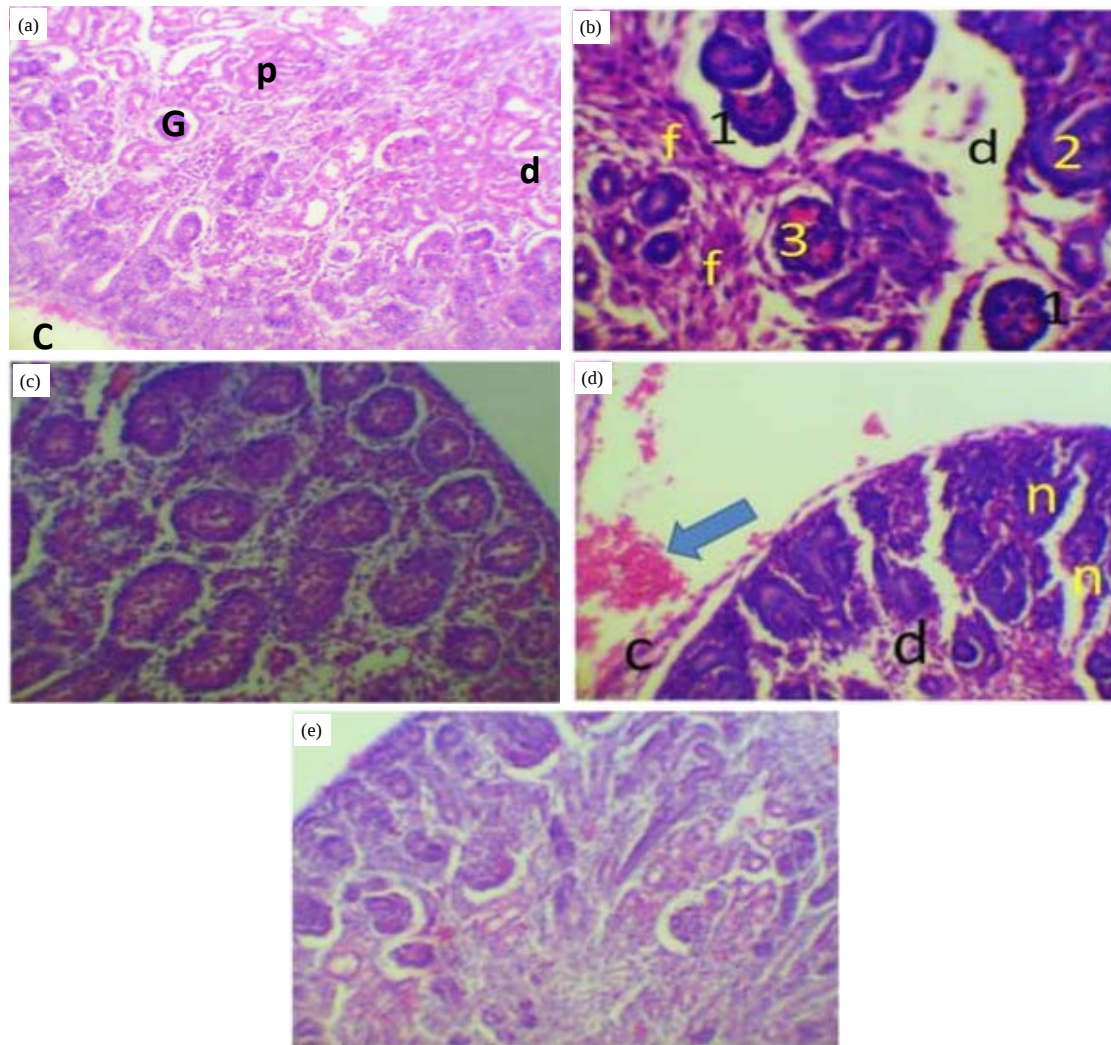


Fig. 2(a-e): Fetal kidney tissue of the control and different treated groups stained with mallory trichrome stain, (a) Group C showing normal architecture of the glomeruli (G), capsule ©proximal (P) and distal (d) convoluted tubules, (b) Group D1 showing malformed (1), hypertrophied (2) or congested (3) glomeruli, atrophied and necrotic CT, numerous degenerated areas (d) and lots of fibroblasts (f), (c) Group D1+P showing somewhat normal appearance of kidney tissue, but few hemorrhagic areas are still detected, (d) Group D7 showing external bleeding around the kidney (arrow), delaminated capsule (c), numerous necrotic CT (n), atrophied glomeruli (G), numerous degenerated areas (d) and many fibroblasts, (e) Group D7+P showing nearly normal architecture of the glomeruli and CTs, but small scattered hemorrhagic can be realized

fibres, small scattered hemorrhagic areas acquired bright red staining affinity in group D1+P (Fig. 3c) and some congested glomeruli acquired bright red staining affinity in group D7+P (Fig. 3e).

DISCUSSION

Chronic hyperglycemia increases oxidative stress factors followed by modifying the function and structure

of proteins and lipids and induces glycoxidation and peroxidation. Thus, hyperglycemia leads to auto-oxidation of glucose, glycation of proteins and activation of polyol mechanism²⁹.

Gestational diabetes mellitus is associated with increased morbidity (hypoglycemia, hypocalcemia, polycythemia, hyperbilirubinemia) and fetal mortality³⁰.

Fetal hyperglycemia is a consequence of maternal hyperglycemia that may destroy growth of β -cells during

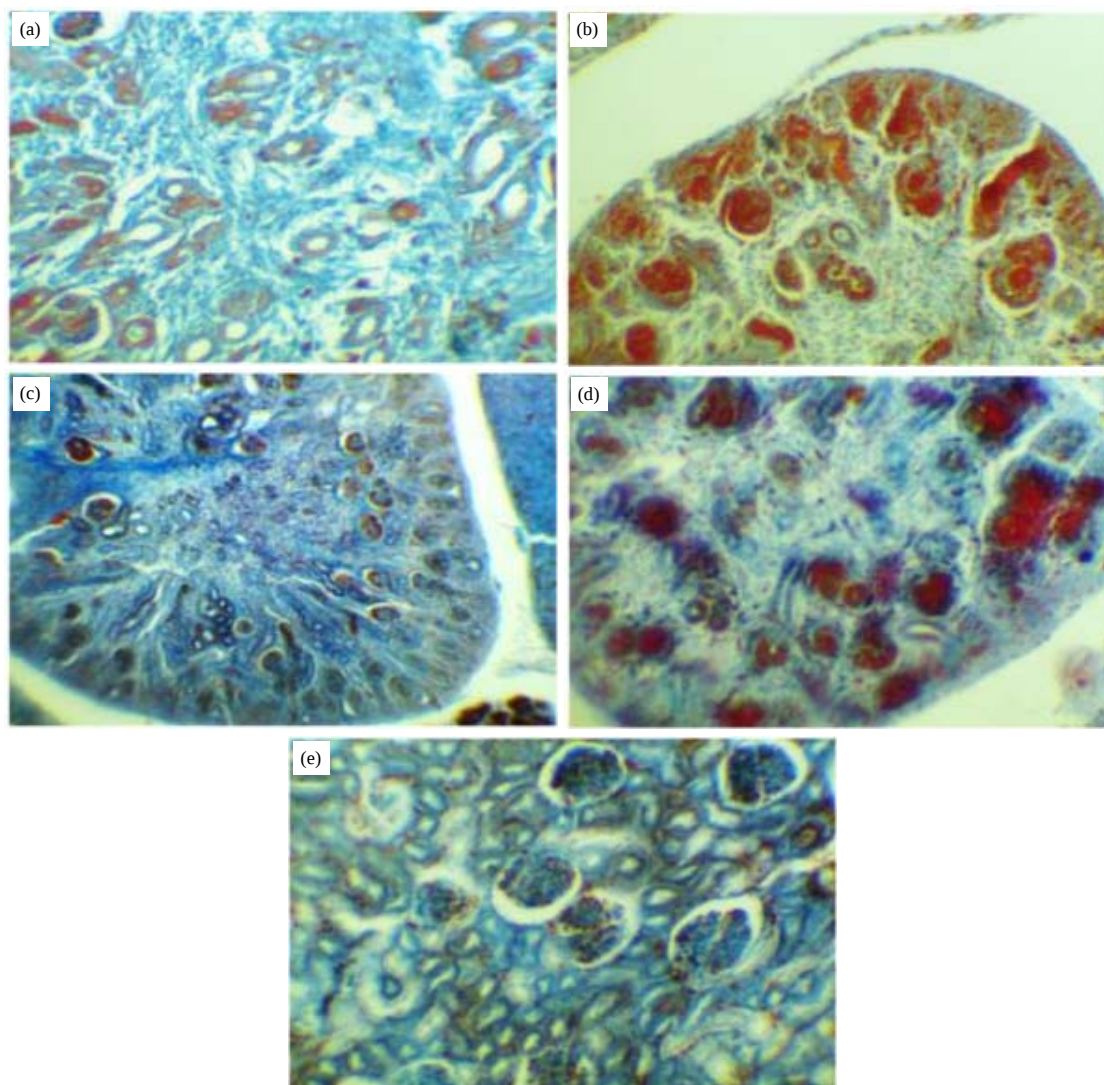


Fig. 3(a-e): Fetal kidney tissue of the control and different treated groups stained with hematoxylin and eosin, (a) Group C showing thin scattered collagen fibres support the capsule, glomeruli and CTs, (b) Group D1 showing reduced collagen fibres in the cortex and medulla with brightly red stained glomeruli and hemorrhagic areas, (c) Group D1 +P showing somewhat normal content of collagen fibres. Small scattered hemorrhagic areas acquire bright red staining affinity, (d) Group D7 showing increased collagen fibres. Brightly red stained hemorrhagic areas, (e) Group D7+P showing nearly normal content of collagen fibres but some congested glomeruli acquire bright red staining affinity

early postnatal period and causes diabetes mellitus in offspring later in life²⁴.

Maternal diabetes mellitus is very important cause leading to pregnancy complications including fetal defects³¹.

The fetus in the first half of pregnancy is exposed primarily to hyperglycemia, which, without secondary hyperinsulinemia, results in slowing the fetal growth. In the second half of pregnancy, hypertrophic islet cells respond to increase glucose level³².

Medicinal plants are dreadful resource for drug development. In recent years, great interest in secondary metabolite production, leads to possibility of altering the production of bioactive compounds via tissue culture technology³³. The medicinal plants have biological activities, low toxicity and economic viability³⁴. In this study we focused on the antioxidant and anti-diabetic role of parsley and its role in reducing diabetes complications.

In the present work, there were no gross malformations in the fetuses of the control rats, but the fetuses of the diabetic

mothers showed retarded fetuses with very thin skin and muscle layer under the skin, absence of eyelid and ear pinna, exencephaly and kyphosis. These results agree with the study of Eid *et al.*³⁵ and Abraham *et al.*³⁶. Diabetes increased rates of fetuses with visceral and skeletal anomalies compared to the control rats according to the study of Damasceno *et al.*³⁷. Fetuses from severe diabetic dams were small at birth and had decreased pancreatic weight³⁸. During pregnancy the fetoplacental endocrine changes showed maternal and fetal effects³⁹. Maternal estrogen, progesterone, adiponectin and leptin levels were related to body weight and insulin sensitivity⁴⁰. Diabetes in pregnancy cases spontaneous abortion, fetal malformation, fetal demise, macrosomia, preeclampsia and neonatal hyperbilirubinemia, among others. In addition, it may increase the risk of obesity and type 2 diabetes in fetuses later⁴¹. Diabetic mothers constitute an unfavorable status for fetal-placental and embryonic development⁴². Diabetes caused higher DNA damage confirming the interaction between hyperglycemia-induced genotoxicity and teratogenesis⁴³. Oxygen and nitrogen species, the products of free radicals, which are dependent on fatty acid oxidation, can induce chromosomal damage in streptozotocin-induced diabetes mellitus⁴⁴.

Parsley extract treatment after induction of diabetes improved reproductive outcomes in the diabetic rats, improved fetal weight and reduced the incidence of fetal malformations. Parsley is one of the medicinal plants that have therapeutic properties for treatment of diabetes mellitus⁴⁵. This may be due to chemical structure of parsley leaf which includes flavonoid⁴⁶, ascorbic acid⁴⁷, these phytochemicals improve total antioxidant capacity, destructive oxygen free radicals and prevents oxidative damage⁴⁸ and anti-urolithiasis²³.

Pregnancy is largely diabetogenic in rats⁴⁹. Unlike other studies where the diabetogenic effect of pregnancy is complicated by other agents like streptozotocin (STZ) and fructose⁵⁰.

The present study showed that the fetal weights were significantly lower in groups D1 and D7 compared to the control group. The fetal rats weight in GDM group were lower than those in the control group²⁵. This decrease may be due to the loss or degradation of proteins structure and that contribute to weight of body and impairment in action of insulin in the conversion of glucose into glycogen³⁶. Diabetes led to thickening of the membranes, limiting the inter villous space and reduced the blood flow and maternal-fetal exchange, thus the flow of blood to the placenta in the diabetic rats was reduced by 50% in late pregnancy, restricting the levels of oxygen and nutrients to the fetus, which can cause decrease in birth weight⁵¹.

After administration of parsley extract the present study recorded a slight improvement in the fetal weight in group D7+P group, but there was a significant decrease in fetuses of group D1+P. Parsley contains flavonoids and quercetin which have numerous protective effects on different tissues⁵².

Increased placental weight and index were detected in the diabetic groups D1 and D7 compared to the control group. Increased weight of placenta is a compensation mechanism which leads to increase the surface area for maternal-fetal exchange. However, this increase in weight of placenta may lead to insufficient fetal nutrition⁵³.

The present study showed that the fasting blood glucose concentrations were significantly increased in the diabetic rats treated with streptozotocin on day 1 and on day 7 of gestation. These results agree with the results of Taiwo *et al.*⁴⁹, Abou Khalil *et al.*¹², Nazari *et al.*²⁴ and Salah *et al.*⁵⁴. The hyperglycemia of the intrauterine environment leads to the functional exhaustion of the pancreas of fetuses, that leads to reduction in insulin secretion, causing impaired fetal growth and increased rates of small pregnancy age (SPA)⁵⁵.

The present study showed improvement in glucose level of groups D1+1 and D1+7. These results agree with those of Abou Khalil *et al.*¹² *Petroselinum crispum* improved hyperglycemia-induced heart and aorta oxidative damage due to its antioxidant activity in the heart and aorta tissue⁵⁶.

Highly significant increase in the urea and creatinine level was observed in the present study in the diabetic groups D1 and D7 compared to the control group. These results agree with those of Eid *et al.*³⁵ and Salah *et al.*⁵⁴. Renal arterial disease and/or cardiac failure in addition to diabetic nephropathy lead to increased serum creatinine. Hyperglycemia leads to kidney damage through glycosylation, release of several cytokines and activation of protein kinase C⁵⁷. In addition, this may be result from failure of the body to excrete products of protein⁵⁸.

Antioxidant properties of parsley are likely to be responsible for its effects⁴⁶. Parsley is one of the most widely used herbal medicines in Latin America medicine, which has been used in clinical settings to treat diabetes complications and its side effects on kidney and liver for years⁵⁹.

The present study recorded an improvement in serum creatinine and urea levels after administration of parsley extract. In a study on diabetic rats with nephropathy, parsley extract improved kidney functions and it was useful in treatment of human diabetic renal disease⁵⁶. This improvement due to improvement of the kidney functions and decreased the excessive loss of albumin in urine in the diabetic rats, because its antioxidants properties have a protective effect against the diabetic nephropathy^{60,61}. Significant decrease was noted in urinary calcium and

proteins and concluded the antiurolithiatic effect of parsley and significant decrease in serum urea, creatinine, uric acid and electrolytes and concluded the nephroprotective effect of parsley on rats²³. A study demonstrated that parsley has large amount of chlorophyll that may decrease the growth of calcium oxalate dehydrate which is considered to be a primary phase in calcium oxalate stone formation¹³.

In this experiment fetal kidney cortex of the control group showed normal architecture of the glomeruli, capsule and CTs with thin scattered collagen fibres in them. Normal fetal kidney examined well-marked lobulation in fetal kidney in early stages of pregnancy, as days of gestation increased, lobulations were less marked⁶².

Histological examination of fetal kidney tissue of group D1 and D7 in the present experiment showed malformed, hypertrophied or congested glomeruli, atrophied and necrotic convoluted tubules, numerous degenerated areas and lots of fibroblasts with external bleeding around the kidney. Reduced collagen fibres in the cortex and medulla with brightly red stained glomeruli and hemorrhagic areas were detected in fetuses of group D1. Diabetes mellitus generates oxidative stress and causes DNA damage to embryo and placenta. The authors speculate that the ability of streptozotocin to generate free radicals in the presence of suitable reducing agents, like reduced glutathione and oxygen⁶³.

Fetal kidney of the diabetic rats showed that the glomeruli were smaller and there were relatively low number of nephrons and there were some evidences of nephron collapse⁶⁴. Epigenetics effects of maternal diabetes mellitus on the offspring have been identified in animal streptozotocin-induced maternal diabetes, in which histone H3 and H4 acetylation of embryonal genes was implicated in neural tube defects⁶⁵. Advanced renal dysfunction and poorly controlled underlying primary kidney disease are all significant risks for adverse maternal, fetal and renal outcomes²⁹.

The kidney sections in diabetes mellitus showed damaged proximal convoluted tubules, glomeruli and interstitial inflammation⁶⁶. Nephropathic changes in the renal tissue of the diabetic rats and attributed the swelling of mitochondria and endoplasmic reticulum of the convoluted tubules and the cell becomes water logged due to swelling of the some organelles⁶⁷. Metabolic changes associated with diabetes led to glomerulosclerosis, glomerular hypertrophy, tubulointerstitial inflammation and fibrosis⁶⁸.

Diabetic kidney disease seems to be one of the most frequent complications of diabetes mellitus. Based on increased free-radical formation and/or diminished antioxidant defenses induced oxidative stress that is implicated in the pathogenesis of diabetic kidney disease. It

induces oxidative stress as well as reactive oxygen species (ROS) formation that attributes to the activation of various downstream signaling cascades leading to structural and functional changes in the kidney²⁹.

Administration of parsley leaf extract in the present study improved the histological architecture of fetal kidney. Somewhat, normal appearance of kidney tissue was noted, but few hemorrhagic areas were still detected with somewhat normal appearance of collagen fibers. The medicinal properties of plants have been investigated in the recent scientific developments throughout the world, due to their potent biological activities, low toxicity and economic viability³⁴. Many studies showed that parsley including flavonoid⁴⁶, ascorbic acid⁴⁷, tocopherol and coumarines⁴⁶, these phytochemicals improve total antioxidant capacity, destructive oxygen free radicals and prevents oxidative⁴⁸. Anti-inflammatory role of parsley extract was detected by several^{69,34}.

Flavonoids can scavenge free radicals and chelate metals for example; pro-anthocyanidin and luteolin to possess antioxidant activities which protect from diabetic kidney disease⁷⁰. Parsley is considered as anti-hypertensive, anti-microbial, anti-diabetic, laxative in digestive tract, balance enzyme activities, increase glutathione in the kidney and clean kidney tissue after nephrotoxicity⁷¹.

CONCLUSION

Fetuses of the diabetic mothers showed some developmental changes, but fetuses of the diabetic mothers which were administrated parsley extract showed somewhat normal morphological development. According to the biochemical, histopathological observations of kidney, the parsley leaf extract succeeded to minimize the drastic changes, which were observed in the diabetic rats and their fetuses. Finally parsley leaf extract has the ability to minimize the damage of hyperglycemia in pregnant rats and their fetuses.

SIGNIFICANCE STATEMENT

This study discovers the parsley that can beneficial for protection from destroy of gestational diabetic mellitus, reduce hyperglycemia in rats and minimize hazards of diabetes in the morphological, anatomical, biochemical and histopathological studies in pregnant rats and their fetuses. This study will help the researcher to uncover the critical areas of parsley extract and its effect on pregnancy and fetuses.

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