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Research Article
Role of PPARγ/Anti-inflammatory Axis in the Protective Effect of Ellagic Acid Against FSD/STZ-induced Gestational Diabetes in Rats

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Abstract

Background and Objective: Ellagic acid (EA) is a natural polyphenol compound with promising anti-diabetic effects. This study examined the safe effects of EA from *Padina boryana* against fatty-sucrosed diet (FSD)/streptozotocin (STZ)-induced gestational diabetes mellitus (GDM), referring to the role of peroxisome proliferator-activated receptor gamma (PPARγ)/anti-inflammatory axis. **Materials and Methods:** Female albino Wistar rats were allocated into three groups. Group I fed with normal diet (ND). Group II and III were fed FSD for 8 weeks (five pre-gestational and three gestational). Rats of group III were administered with a daily oral dose of 50 mg kg^{-1} EA 1 week before mating onward. At the 7th day of the gestation, to induce GDM, FSD-fed dams were injected intraperitoneally with STZ (25 mg kg^{-1} b.wt.). **Results:** Pre-mating administration of EA controlled the body weight loss, hyperphagia, glucose intolerance and insulin resistance during the gestational period than in diabetic dams. EA also reduced levels of total cholesterols, triglycerides, hepatic lipid peroxidation, fructosamine and nitric oxide levels, while it significantly increased levels of high-density lipoprotein-cholesterol, liver glycogen, glutathione and catalase activity. In addition, EA supplementation markedly attenuated serum levels of tumor necrosis factor-alpha and leptin while adiponectin level was elevated. These effects coincided with up-regulation of the visceral adipose tissue PPARγ expression at term pregnancy. Besides, EA nearly normalized number of viable fetuses, implantation loss sites as well as fetal insulin and glucose levels. **Conclusion:** EA safely ameliorates gestational hyperglycemia in rats via potential association of PPARγ and anti-inflammatory biomarkers that suppress the oxidative stress status.

Key words: Ellagic acid, gestational diabetes, anti-diabetic action, PPARγ, inflammatory cytokine, oxidative stress

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Competing Interest: The authors have declared that no competing interest exists.

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

INTRODUCTION

Diabetes mellitus (DM) is a chronic lifelong metabolic disease characterized by hyperglycemia resulting from imperfections in insulin secretion, action or both[1]. Gestational diabetes mellitus (GDM) is the most common pregnancy-related illness. It affects 1.4-25.5% of the pregnant population/year depending on the ethnicity of the population studied[2]. The GDM is defined as glucose intolerance of variable severity that first recognized during pregnancy[1]. The GDM is associated with an elevated risk of maternal cardiovascular complications and type 2 diabetes (T2D) later in life and the offspring to increased rates of perinatal hypoglycemia, jaundice, respiratory distress and long-term risk of diabetes and obesity[3].

Pregnancy is associated with a complex molecular alteration in the adipose tissue including critical changes in the transcription factor peroxisome proliferator-activated receptor gamma (PPARγ)[4]. The PPAR is commonly expressed in the adipose tissue, placenta and the immune system and considered a key manager of glucose and lipid metabolism, stimulates preadipocyte differentiation, increases the storage of fatty acids in adipocytes, regulates adipokines involved in insulin resistance and thus, increasing insulin sensitivity[5].

Insulin is the optimal choice for managing gestational diabetes if dietary and lifestyle trials fail to maintain normoglycemia. However, this therapy necessitates multiple daily injections, produces maternal hypoglycemia and increases the appetite and body weight that may downgrade patient adherence[6]. Synthetic oral hypoglycemic agents administration (mainly metformin and glyburide) which are usually recommended for T2D instead of insulin appears to be tempting, but they founded to have dermatological and gastrointestinal side effects including nausea, diarrhea and vomiting with an incidence rate of 63% rather than being costly[7].

Ellagic acid (EA) is a polyphenol isolated from *Padina boryana* Thivy by chromatographic ways. It has a broad spectrum of pharmacological properties including anti-oxidant, anti-microbial, anti-viral, anti-apoptotic and anti-carcinogenic activities[8]. Previous studies by Malini *et al.*[9] and Jadhav and Puchchakayala[10] have demonstrated the hypoglycemic potential of EA in type 1 and type 2 diabetic rats, respectively. Up to now, no attention has been paid to the role of EA in controlling the gestational hyperglycemia and its effect on maternal outcome and fetal glycemia. Thus, the current study aimed to clarify the protective effect of EA against FSD/STZ-rat model of gestational diabetes focusing on the role of PPARγ/anti-inflammatory pathway.

MATERIALS AND METHODS

Experimental materials: n-Hexane, streptozotocin, 5,5'-dithiobis-2-nitrobenzoic acid (DTNB), glutathione (GSH), thiobarbituric acid (TBA), meta-phosphoric acid, 1,1,3,3-tetramethoxypropane, pyrogallol, RNA later, ethidium bromide and agarose were purchased from Sigma Chemical Co. (USA). Other chemicals used in this study were of analytical grade and provided from standard commercial supplies.

Padina boryana samples were collected from the eastern coast of the Red Sea, Safaga, Egypt. A voucher specimen (No. BuPD 37) was deposited in Pharmacognosy Department, Faculty of Pharmacy, Fayoum University, Egypt. Dried samples (0.5 kg) were soaked in 70% ethanol at room temperature for 72 h and by the helping of rotary evaporator, soxhlet apparatus and TLC analysis 7 fractions were yielded. Further fractionation was processed using silica gel column giving three sub-fractions from fraction 6. Antidiabetic assay recorded that sub-fraction (F 6, 3) was the most effective one. It contained a mixture of two compounds, the major one was purified to yield a pure compound (36.8 mg); EA.

Female albino Wistar rats (*Rattus norvegicus*) weighing about 100-120 g were obtained from the animal house of VACSERA Co., Helwan, Egypt. Rats fed with two types of diets either normal diet (ND) or fatty-sucrose diet (FSD) and allowed to drink water *ad libitum*. The composition of both diets was illustrated elsewhere[11]. All animal experiments were approved by the Institutional Animal Care and Use Committee (IACUC), Beni-Suef University, Egypt (BSU/FS/2015/11).

Experimental design: The study design is described in Fig. 1. The experiment was carried out in labs of Faculty of Science, Beni-Suef University, for about 5 months. A total of 60 albino Wistar rats were randomly classified into three groups (20 animal/group) as follows:

Group I : Fed on ND. Four weeks after dietary manipulation rats were received 0.5% dimethyl sulfoxide (DMSO) as a vehicle by oral gavage daily to the end of the experiment

Group II : Fed on FSD. Four weeks after dietary manipulation rats were received the vehicle by oral gavage daily to the end of the experiment

Group III : Fed on FSD. Four weeks after dietary manipulation rats were received EA (50 mg kg^{-1} b.wt., dissolved in 0.5% DMSO) by oral gavage[10] daily to the end of the experiment

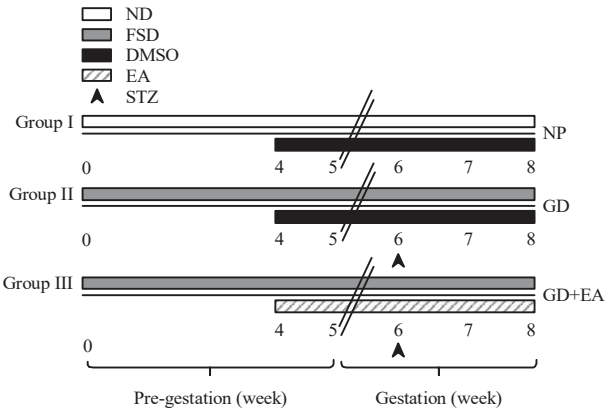

Fig. 1: *In vivo* experimental design. ND: Normal diet, FSD: Fatty-sucrosed diet, DMSO: Dimethyl sulfoxide, EA: Ellagic acid, NP: Normal pregnant, GD: Gestational diabetic, GD+EA: Gestational diabetic pre-treated with ellagic acid, STZ: Streptozotocin

After five weeks from the onset of the experiment, rats of all groups were mated overnight with males. Positive vaginal smear checked in the morning indicated the first day of pregnancy. The time before mating denoted the pre-gestational period while that after mating denoted the gestational period.

At the 7th day of pregnancy, dams were fasted for 16 h and those of groups II and III were i.p. injected with STZ (25 mg kg^{-1} b.wt. in citrate buffer; pH 4.5)[11,12], while those of group I were injected only with the citrate buffer. At the 21st day of gestation, overnight fasted dams were sacrificed under light diethyl ether anesthesia where all measured parameters were denoted to main three groups (n = 10, each):

- Normal pregnant group (NP): Received ND
- Gestational diabetic group (GD): Received FSD/low dose of STZ
- Gestational diabetic group pre-treated with ellagic acid (GD+EA): Received FSD/low dose of STZ and pre-treated with EA (50 mg kg^{-1} b.wt.)

Blood and tissues collection: Blood samples were collected from the jugular vein of each rat, centrifuged and sera were kept at -40°C for future analyses. After dissection of rats, visceral adipose tissue was preserved in RNA later and stored at -40°C for the gene expression analysis. Maternal liver samples were excised for estimation of glycogen content, anti-oxidants and oxidative stress parameters. All dams were subjected to OGTT at the 20th day of gestation. Blood samples were withdrawn from the lateral tail vein of animals fasted for 6-8 h and after 30, 60, 90 and 120 min of oral gavage of glucose solution (3 g kg^{-1} b.wt.)[12].

Determination of biochemical assays: Serum glucose was detected using reagent kit procured from Spinreact Co. (Spain) while insulin concentration was estimated by the sandwich ELISA according to the manufacturer's instructions of a rat kit obtained from BioSource Europe S.A. (Belgium). Hepatic glycogen content was measured in the tissue homogenate of each rat by the method of Seifter *et al.*[13], while serum triglycerides, total cholesterol, high-density lipoprotein (HDL)-cholesterol and fructosamine levels were determined according to reagent kits purchased from Spinreact Co. (Spain). TNF-α, leptin and adiponectin were estimated using rat reagent kits bought from RayBiotech, Inc. (USA). The steps were carried out according to the manufacturer's instructions. Malondialdehyde (MDA) as lipid peroxidation biomarker and nitrite as nitric oxide (NO) biomarker were detected in the liver tissue homogenate by the method of Yagi[14] and the NO-kit (Biodiagnostic, Egypt), respectively, as key oxidative stress indicators. In contrast, GSH (as a non-enzymatic antioxidant) and the antioxidant enzyme catalase (CAT) were investigated by methods of Beutler *et al.*[15] and Sinha[16], respectively.

RNA extraction and gene expression analysis: Extraction of RNA from the visceral adipose tissue was performed using TriFast™ reagent (PeQlab, Germany). The RNA was then purified and quantified spectrophotometrically. Using reverse transcriptase-polymerase chain reaction (RT-PCR) kit (Promega, USA), cDNA was produced from 2 µg RNA. In 25 µL PCR amplification reaction, cDNA was used for the detection of PPARγ using Green master mix (Promega, USA) and primers designed by Midland Certified Reagent Company Inc. (USA). The forward primer is 5'-CCCTGGCAAAGCATTTGTAT-3' and the reverse one is 5'-ACTGGCACCCTTGAAAAATG-3' to give an amplicon size of 222 bp. The β-actin was selected as an internal control with primers have a forward one of 5'-TGGGACGATATGGAGAAGAT-3' and a reverse one of 5'-ATTGCCGATAGTGATGACCT-3' to give an amplicon size of 522 bp. The PCR reaction was performed using T100™ thermal cycler (Bio-Rad Laboratories, USA) with conditions of initial denaturation at 95°C for 5 min, 35 cycles [94°C (1 min) for denaturation, 55°C (1 min) for annealing and 72°C (1 min) for extension] and finally 72°C (5 min) to complete the extension reaction. On 1.5% agarose gels containing ethidium bromide, PCR products were subjected to electrophoresis. Gel documentation system was used to capture images from the electrophoresed gels. Band intensities were analyzed using Phoretix 1-D densitometry software v.11 (TotalLab Ltd., UK) after being normalized with those of β-actin. Values presented as % mRNA relative to control.

Statistical analysis: Data are presented as means±SEM of 6 rats. Results of maternal serum glucose and insulin levels, OGTT, body weight and food intake were analyzed using the two-way analysis of variance (ANOVA) where the fixed factors were defined as 'group' and 'time'. One-way ANOVA test followed by Tukey-Kramer test for *post hoc* analysis was performed to further analyze the significant differences in the means between the groups. The $p<0.05$ were considered statistically significant. All statistical analyses were performed using the SPSS v.22 software (SPSS Inc., Chicago, USA).

RESULTS

Effect of EA on body weight changes and food intake behavior: Figure 2a indicated an obvious increase in the body weight of FSD-feeding rats of group II and III during the pre-gestational period as compared to ND-fed rats of group I. Besides, dams of group II showed a state of hyperphagia after STZ injection mainly at the late-gestation (Fig. 2b). Oral administration of EA to rats of group III from the beginning of the 5th pre-gestational week onward protected them from the body weight loss after STZ injection and controlled their food intake.

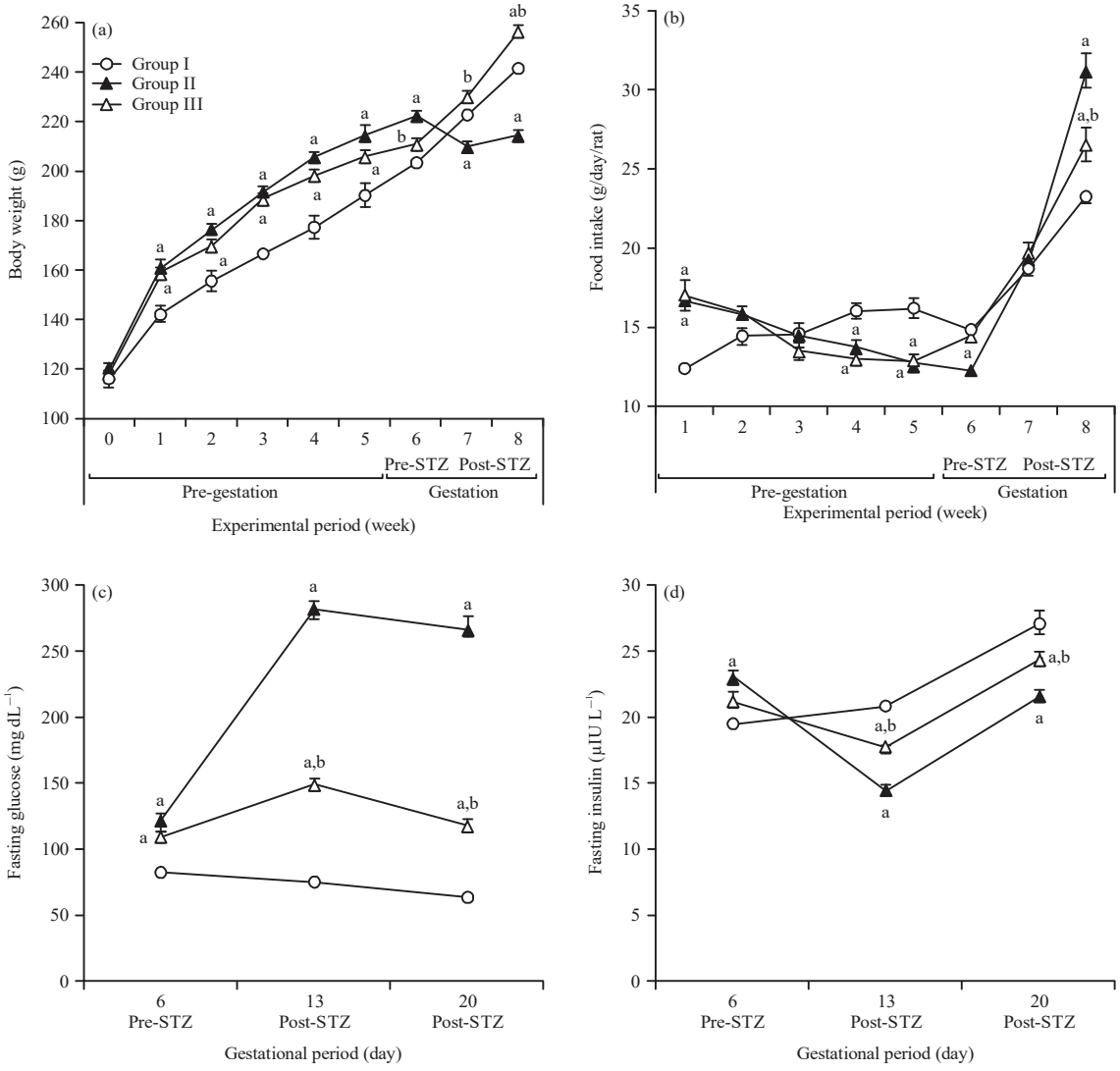

Fig. 2(a-d): (a) Represented the body weight changes during the pre-gestational and gestational periods, (b) Represented the food intake changes during the pre-gestational and gestational periods, (c-d) Represented the fasting serum glucose and insulin levels during the gestational period, respectively

Results are expressed as Mean±SEM. [a]$p<0.05$ vs. group I, [b]$p<0.05$ vs. group II, compared to the respective time

Effect of EA on biochemical parameters: Although serum glucose, insulin and leptin levels of FSD-fed rats showed significant elevation at the end of the Pre-gestational period compared to normal rats (Table 1), these parameters appeared near normal ones for EA-administrating rats at the late gestation (Fig. 2c, d and Table 2). Moreover, OGTT showed that EA administration caused significant hypoglycemia when compared to the respective hyperglycemic GD-group (Fig. 3). Maternal data in Table 2 shows significant depletion ($p<0.05$) in the hepatic glycogen content and serum HDL-cholesterol of GD-dams with a subsequent increase in serum fructosamine, triglycerides and total cholesterols levels. EA treatment ameliorated these parameters and interestingly increased HDL-cholesterol than normal group. The results revealed significant elevation in hepatic MDA and nitrite levels in GD-group when compared to NP-one. Moreover, the liver of GD-dams observed a significant depletion in GSH content with a concomitantly reduced activity of the anti-oxidant enzyme; CAT. Otherwise, EA attenuated both MDA and nitrite production and revealed an increase in GSH concentration and CAT activity compared to diabetic one.

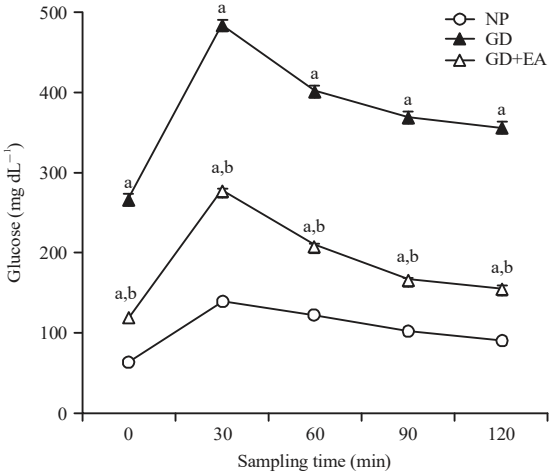

Fig. 3: OGTT at the 20th day of gestation

[a]p<0.05 vs. NP, [b]p<0.05 vs. GD compared to the respective time. NP: Normal pregnant, GD: Gestational diabetic, GD+EA: Gestational diabetic pre-treated with ellagic acid

Table 1: Serum glucose, insulin and leptin levels at the end of the pre-gestational period

Groups	Glucose (mg dL^{-1})	Insulin (μIU mL^{-1})	Leptin (pg mL^{-1})
I	88.23±2.06	16.03±0.84	503.28±21.20
II	118.49±5.32[a]	20.61±2.01[a]	767.30±8.63[a]
III	112.00±3.03[a]	19.52±0.90[a]	719.96±9.19[a,b]

Results are presented as means±SEM of six rats. [a]p<0.05 vs. group I, [b]p<0.05 vs. group II

Effect of EA on PPARγ, the inflammatory biomarkers and maternal reproductive outcome: Figure 4a and b revealed a significant decrease in the visceral adipose tissue PPARγ mRNA expression level in FSD/STZ-gestational diabetic rats in comparison with that of normal pregnancy. Treatment with EA induced a significant amelioration in PPARγ gene expression, as well as in serum leptin and TNF-α levels which was elevated in GD-group (Table 2). On the other hand, adiponectin was declined significantly in diabetic dams and EA nearly normalized it (Table 2). Gestational diabetes increased the fetal serum insulin and glucose levels markedly as compared to those of NP-dams. Interestingly, oral administration of EA revealed profound amelioration of the maternal reproductive performance and control the fetal glycemic state.

Table 2: Impact of ellagic acid administration on maternal and fetal biomarkers at term pregnancy

Parameters	NP	GD	GD+EA
Maternal parameters			
Liver glycogen (mg g^{-1} tissue)	12.69±0.57	3.55±0.19[a]	8.50±0.28[a,b]
Fructosamine (mmol L^{-1})	45.39±3.05	185.70±5.25[a]	89.82±3.46[a,b]
Triglycerides (mg dL^{-1})	58.72±1.44	189.64±1.34[a]	59.28±1.230[b]
Total cholesterols (mg dL^{-1})	81.12±1.45	185.13±2.51[a]	118.58±1.51[a,b]
HDL-cholesterol (mg dL^{-1})	58.06±1.54	52.52±1.18[a]	76.04±2.12[a,b]
Leptin (pg mL^{-1})	574.65±46.38	1265.40±42.15[a]	915.30±23.56[a,b]
TNF-α (pg mL^{-1})	210.77±4.42	374.40±7.19[a]	216.67±4.83[b]
Adiponectin (pg mL^{-1})	946.68±4.54	693.95±16.73[a]	915.52±24.04[b]
MDA (nmol g^{-1} tissue)	54.63±1.64	120.93±2.18[a]	89.29±1.91[a,b]
NO (nmol g^{-1} tissue)	82.36±0.88	92.52±1.33[a]	80.64±0.65[b]
GSH (nmol/100 mg tissue)	450.38±13.72	237.18±9.94[a]	338.00±9.83[a,b]
CAT ($K\times10^{-2}$)	63.61±1.11	31.62±1.01[a]	45.78±1.13[a,b]
Fetal parameters			
Live fetuses	8.75±0.52	4.25±0.22[a]	7.30±0.19[a,b]
Implantation loss	3.50±0.2	9.56±0.38[a]	3.55±0.11[b]
Fetal weight (g)	3.08±0.03	3.40±0.10	3.36±0.40
Fetal glucose (mg dL^{-1})	42.94±1.46	161.50±4.12[a]	86.44±2.60[a,b]
Fetal insulin (μIU mL^{-1})	3.60±0.14	6.20±0.16[a]	4.98±0.12[a,b]

Results are presented as Means±SEM of 6 rats. [a]p<0.05 vs. NP, [b]p<0.05 vs. GD. NP: Normal pregnant, GD: Gestational diabetic, GD+EA: Gestational diabetic pre-treated with ellagic acid, HDL-cholesterol: High-density lipoprotein-cholesterol, TNF-α: Tumor necrosis factor-alpha, MDA: Malondialdehyde, NO: Nitric oxide, GSH: Glutathione, CAT: Catalase

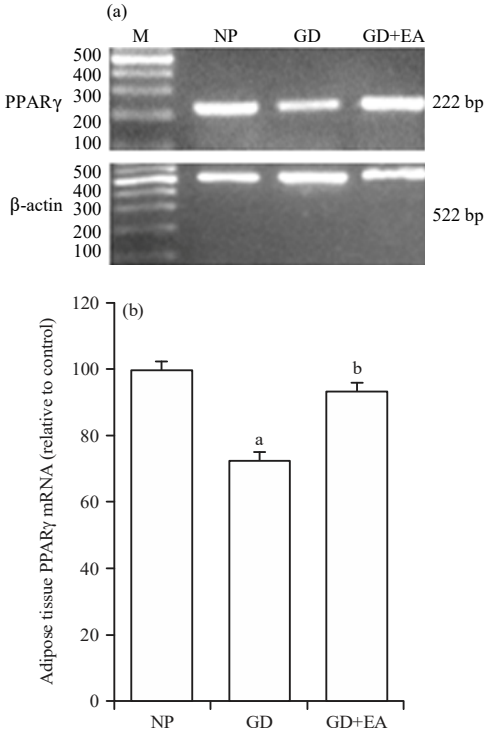

Fig. 4(a-b): RT-PCR analysis of visceral adipose tissue PPARγ and β-actin expression, (a) Gel photograph depicting representative PCR products and (b) Corresponding densitometric analysis of PCR products

[a]p<0.05 vs. NP, [b]p<0.05 vs. GD, M: DNA marker. NP: Normal pregnant, GD: Gestational diabetic, GD+EA: Gestational diabetic pre-treated with ellagic acid

DISCUSSION

The current data showed that the increase in the body weight of FSD-feeding rats during the pre-gestational period was accompanied with a significant decrease in the food intake as a result of a profound increase in serum leptin level. In addition, feeding diet rich in fats induced a state of glucose intolerance accompanied by an increase in serum insulin release[17] which may be discussed through the glucose-fatty acid cycle[18]. Also injection of low dose of STZ at mid-gestation caused moderate destruction of pancreatic β-cells via generation of reactive oxygen species (ROS) which induce apoptosis and suppression of insulin biosynthesis[19]. As it being a polyphenolic compound, EA acts as a ROS-scavenger and protecting dams from the body weight loss after STZ injection. Moreover, EA induced a noticeable decrease in the serum glucose concentration as compared to diabetic rats. A possible mechanism of its hypoglycemic effect may be via its antioxidant properties[9]. Glycogen considered the essential intracellular storable form of glucose and its level in different tissues especially in the liver reflect the direct action of insulin activity[20]. Oral administration of EA significantly increases hepatic glycogen level secondary to the reactivation of the glycogen synthase system as a result of increased insulin secretion. As known, elevated blood glucose level for a time was previously demonstrated to make glucose molecules permanently combine with blood proteins in a process called glycation[21]. So, serum fructosamine (a putative measure of glycated proteins) was increased in GD-dams and EA administration induced an obvious decrease of of it possibly by the increased insulin secretion and sensitivity.

Current study revealed a marked increase in serum total cholesterols and triglycerides (TG) levels with a reduction in HDL-cholesterol in FSD/STZ-diabetic dams due to increased dietary triglycerides and cholesterol intake. In addition, it has been mentioned that dysfunction of lipoprotein lipase (LPL) in the state of insulin deficiency contributes to hypertriglyceridemia due to impaired catabolism of triglyceride-rich particles and decreased TG uptake in peripheral tissues[22]. The significant amelioration of the serum lipid variables in EA-treated dams might have been due to its insulin-sensitizing actions[8].

Insulin depletion and sustained hyperglycemia that induced by β-cell dysfunction in DM were considered as principal mediators of increased ROS generation[23]. This study elucidated a significant increase in MDA levels in liver GD-dams. Moreover, liver NO is markedly elevated in diabetic dams. NO is a free radical produced in mammalian cells and is involved in the regulation of various physiological processes but its excessive production is associated with several diseases[24]. Moreover, ROS augment gene expression of nuclear factor-κB (NF-κB) and inflammatory mediators[25]. The current study hypothesized that the oral administration of EA significantly protects against the formation of lipid peroxides through its potent free radical-scavenging activity and its capability to compete with oxygen to react with NO to suppress nitrite and peroxynitrite production[26]. In contrast, the present data showed that the liver of GD-dams revealed a significant decrease in GSH content with a concomitant reduction in CAT activity. Regeneration of GSH from its oxidized form (GSSG) required NADPH that necessitates an increase in glucose oxidation through the pentose phosphate cycle[27]. As a result of insulin deficiency in GD-dams, level of NADPH is decreased and thereby that of GSH provoking the oxidative stress state. Moreover, hyperglycemia during pregnancy causes glycation of CAT enzyme making it inactive. The antioxidant activity of EA referred to its ability to control the glycemic state and inhibiting the glycation of the antioxidant enzymes.

The present study elucidated a significant decrease in the visceral adipose tissue PPARγ mRNA expression in

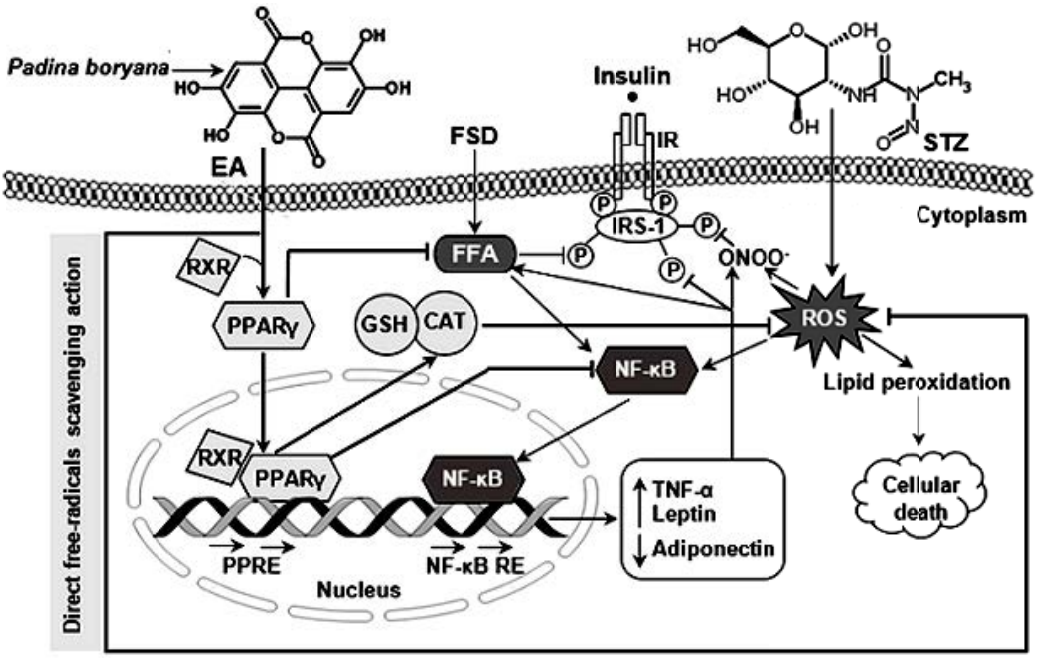

Fig. 5: Schematic depictions of the protective mechanisms of EA against FSD/STZ-induced gestational diabetes. EA: Ellagic acid, FSD: Fatty-sucrosed diet, STZ: Streptozotocin, IR: Insulin receptor, IRS-1: Insulin receptor substrate-1, P: Tyrosine phosphorylation, PPARγ: Peroxisome proliferator activated receptor gamma, RXR: Retinoid X receptor, PPRE: Peroxisome proliferator response element, CAT: Catalase, GSH: Glutathione, ROS: Reactive oxygen species, $ONOO^-$: Peroxynitrite, FFA: Free fatty acids, NF-κB: Nuclear factor-κB, NF-κB RE: Nuclear factor-κB response element, TNF-α: Tumor necrosis factor-alpha

FSD/STZ-gestational diabetic group in comparison with that of normal pregnancy. When activated, PPARγ heterodimerizes with retinoid X receptor (RXR), binds to specific response elements (PPREs) and promotes the expression of target genes[28]. The PPARγ performs its action on glucose and lipid metabolism by controlling energy homeostasis in adipose tissues and decreasing plasma free fatty acids (FFA) concentration[5]. It, also, has been shown to induce anti-inflammatory responses through inhibiting the activation of NF-κB resulting in attenuation of proinflammatory cytokines production[29]. Moreover, upon activation, PPARγ trans-locates into the nucleus and promotes expression of CAT anti-oxidant enzyme through PPREs containing the canonical direct repeat 1 located 12 kb far from the transcription initiation site[30]. In this context, EA may exert its insulin-sensitizing effect via up-regulation of PPARγ that alleviating lipotoxicity, enhancing anti-oxidant defenses and preventing the production of pro-inflammatory cytokines.

The present findings revealed significant elevation in circulatory leptin and TNF-α levels which are strongly correlated with insulin resistance in GD-dams. The elevated level of leptin in GD-dams may perform a hyperleptinemia state and leptin resistance which directly embroiled in insulin resistance via a number of mechanisms including impairment of IR-tyrosine phosphorylation (P), rising peroxynitrite-mediated oxidative stress and activating immune cells-proliferation that control the release of TNF-α[31]. TNF-α has been shown to mediates lipolysis, increases circulating FFA and stimulates IR-serine phosphorylation which collectively contributes to the pathogenesis of insulin resistance[32]. In contrast, serum adiponectin level was reported to be in agreement with insulin sensitivity and its reduced level of GD-dams is associated with the insulin resistant state[33]. Treatment with EA markedly decreased serum levels of leptin and TNF-α and increased circulating adiponectin confirming its anti-inflammatory efficacy.

Regarding the maternal outcome, the current data showed a reduction in the number of viable fetuses consequently to an increased loss rate of embryonic implantation, as a result of the hyperglycemia-induced reproductive disturbances[11]. As the placental transfer of glucose is carried out according to concentration-dependent kinetics[34], fetuses of GD-rats showed an elevated serum glucose level which stimulated the fetal pancreatic beta-cell hyperplasia and hyperinsulinemia. Oral administration of EA protected the fetuses from diabetes-induced damages and alleviated the maternal reproductive performance.

CONCLUSION

The present study demonstrated the safe protective action of EA on GDM. EA effectively improved glucose tolerance of GD-dams by potentiating insulin secretion, sensitivity and action mainly through mechanisms associated with activation of PPARγ that resulting in attenuation of excessive inflammatory response and enhancement of anti-oxidant defenses. Additionally, EA controls fetal glycemia and alleviates the reproductive performance.

SIGNIFICANCE STATEMENT

The study revealed that ellagic acid had a beneficial effect against gestational diabetes and its complications. This study will help the researcher to uncover the critical areas of anti-diabetic mechanisms of ellagic acid related to activation of PPARγ, attenuation of the excessive inflammatory response and enhancement of anti-oxidant defenses which may open the gate for researchers to complete the pharmacological and clinical studies.

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