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Original Article

Safawi Date Extract Ameliorated Diabetogensis and Nephrotoxicity Induced by Propyl Paraben in Rats

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ABSTRACT

Objectives: The Parabens are synthetic compounds used as antibacterial and antifungal preservatives in many products. The nephrotoxicity and diabetogenic development during exposure of rats to propyl paraben and role of of *Safawi* Date Extract (SDE) supplementation were investigated. **Materials and Methods:** Male Wistar albino rats were assigned into five groups; (6 rats each). Group I served as the control while groups II-IV were given 100, 200, 300 mg/ kg bw/day propylparaben respectively. Group V; rats received 300 mg propyl paraben and treated with 100 mg SDE for four weeks. **Results:** Data obtained showed that rats given propyl paraben at 100 mg/kg b.w showed a non significant changes in the levels of glycated Hemoglobin (HbA_{1c}), Malondialdhyde (MDA), creatinine, glucose, insulin, antioxidant enzyme activities and GSH content. However, propyl paraben at 200 or 300 mg/kg b.w after 3 weeks, showed a significant elevated HbA_{1c}, MDA, fasting blood glucose, creatinine levels (p<0.001) while insulin level, were significantly reduced (p<0.001). The antioxidant enzymes activities (GPx, Grase, SOD, Catalase) were reduced in rats given propylparaben versus control. Treatment of rats with SDE ameliorate these abnormal changes. It was concluded that flavonoids (epicatechin, catechin and procyanidin) from SDE showed protective effect against abnormal variability induced by propylparaben by enhancing antioxidants activities, reduces lipid peroxidation and insulin sensitivity. **Conclusion:** Alarming the consumers for uses, the products contain propyl paraben for its toxic effect and diabetogenic effect. Identifying the mechanism of diabetogensis due to exposure of propylparaben for long time.

Keywords: Propylparaben, Insulin Resistance, date flavonoides, Antioxidant, Rats.

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INTRODUCTION

The incidence of diabetes and nephrotoxicity caused by environmental pollution is still a challenge of different researchers over the world. Environmental pollution due to Polycyclic Aromatic Hydrocarbons (PAH) can cause disruption of endocrine system and hormonal imbalance. PAH can bind to intracellular receptors, affecting DNA integrity and transcriptional factors and increased risk of some cancer development.[1] The environmental factors including pesticides, plastics, detergents, industrial and synthetic chemicals. The Parabens are synthetic compounds used as antibacterial and antifungal preservatives in many products as foods, drugs and cosmetic.[2] Parabens also used as a preservative in ointments, antibiotics and antiseptic sprays. The margin of safety for parabens is 1.2 mg/ kg body weight daily in adults and 0.3 mg in children. Some parabens have weak anti-androgenic activity *in vitro* and *in vivo* and are categorized as endocrine disruptive agent.[3] It was reported that, when methyl paraben or iso-butyl paraben or n-butyl paraben are administrated orally, 80.5-85.3% of their metabolites are excreted within the first 24 hr.[4] Long term exposure to parabens as in cosmetics, food and medicines lead to accumulation in the body tissue and caused disturbance in physiological pathways.[5] Parabens are metabolized through phase I reaction in liver by hydroxylation followed by phase II reaction via conjugation with glucoronate or sulfate conjugates.[6]

The rate of exposure to propylparaben is 1.5 times higher in children than adults due to the toys contaminated with it.[7] Also, paraben-containing skin care products for babies is more than expected due to penetration via epidermal layers. It was reported that, when paraben taken via inhalation, it causes irritation of the gastrointestinal tract when taken orally, redness, pain, allergic reactions in eyes and skin.[8]

Insulin resistance and diabetes is the most challenge disease worldwide that focus on the prevention or therapeutic protocol without complications. It is mediated by inflammatory mediators in different tissues as kidney β -cells of pancreas and development of diabetes.[9] It was reported, that, low antioxidant capacity of

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tissues are vulnerable to free radicals and oxidative damage. The kidney and Islets of Langerhans in pancreatic tissue that produce insulin, while α cell, delta and epsilon cells produce glucagon, somatostatin and ghrelin, respectively.[10] The coordination of these hormones play an important role in glucose homeostasis. Previous study reported that some chemicals could cause oxidative stress that resulted in decreased insulin production and development of diabetes. HOMA-IR is indicator for insulin resistance.

Date palm is considered as basic food for several cultures over thousands of years and they are still consumed widely all over the world. Date palms farming is concentrated in the Middle East and North Africa. Over 7 million tons of dates are produced annually, but only about 10% enter world trade is consumed locally. *Phoenix dactylifera* L. (date palm) is diversified in about 400 different cultivars.[11] The date palm is a monocotyledon plant with fruits that go through the stages of *hababauk, kimri, khalal, rutab*, and *tamer* during ripening. The main constituents of date include water, sugar, protein, fat, pectin, crude fiber, and polyphenols.[12] Especially the polyphenols have been recognized as strategically important as anti-diabetic, anti-inflammatory, anxiolytic, anti-spasmodic, hepato-, gastro- and nephron-protective and antiatherogenic nutrient that is specifically richly concentrated in the peel and seeds, reaching highest polyphenol concentrations in the *khalal* stage compared to the fully mature *tamer* stage, regardless of cultivar.[13] Polyphenol contents vary 10-fold between 2-20 g/kg dry weight which increases further under long-term storage conditions. Different cultivars of dates In Saudi Arabia including the economically most important varieties *Khodry, Khalas, Ruthana, Sukkari, Sefri, Safawi, Ajwa* and *Hilali*, each separated by seeds and peels (epicarp), and harvested at the *khalal* stage and after cold storage under which polyphenolic contents are known to be further increasing.

To decrease prevalence of diabetes due to environmental pollution we determined the critical duration and doses taken during exposure of propylparaben for development of insulin resistance and diabetogensis in ratsThe rational of this study to investigate the anti-diabetogenic effect of flavonoids extracted from *Safawi* Date Extract (SDE) against toxicity of propylparaben in rats.

MATERIALS AND METHODS

Safawi Date Extract (SDE) preparation

Fresh *Safawi* dates was obtained from date market, Jeddah, Saudi Arabia. Briefly, the tissue part of the Safawi date was (100 g) was homogenized in ethanol 80% at a ratio of 1:1 (w/v) and shaken for 6 hr, centrifuged at 10,000 rpm for 10 min, filtered and concentrated by a rotary evaporator at 20°C and low pressure. The extract was dired by lypholization and stored in -20°C until use in experiments.[14]

Chromatographic identification of *Safawi* date flavonoids by gas chromatography/mass spectrum (GC-MS)

The extract (1 mg) was dissolved in 1 mL acetonitrile and injected into an Agilent 6530 mass spectrometer, C18 1.0 mm×50 mm (2.6 µm) column and the mobile phase (A) 10%-90% (B) 7.5 min gradient (mobile phase A: water with 0.1% acetic acid, mobile phase B: Acetonitrile with 0.1% acetic acid).

Experimental design

This study was carried out on thirty male Wister albino rats weighing 120-150 g were obtained from the animal house, KFMRC, KAU, Jeddah, Saudi Arabia. The animals handling was approved by KAU Research Ethics Committee. Propylparaben was obtained from Fluka Company with purity (99.93%). It was dissolved in DMSO. The animals were divided into five groups (each 6 rats). Group I; Control received the vehicle solution (DMSO). Rats in groups (II-IV) received propylparaben orally at doses 100, 200 and 300 mg/kg body weight/day) according to Soni *et al.*[15] respectively for 4 weeks. Group V: rats received 300 mg/kg body weight/day propylparaben and 100 mg/kg *Safawi* Date Extract (SDE). The dose of date extract was given according to Saleh *et al.*[16]

Biochemical analysis

At the end of experiment, rats were overnight fasted and blood samples were withdrawn from all groups under light anesthesia by thiopental. Blood was divided to two parts, first part taken on heparin for plasma separation while the other part on plain tube for serum separation.

The glycated Hemoglobin (HbA_{1c}) was determined in whole blood sample by method assay kit from Abbexa, UK. Fasting blood glucose and creatinine were determined by colorimetric method using Biodiagnostic kit, Cairo, Egypt. Insulin, was determined by ELISA technique using kits from ABCAM, USA.

Insulin resistance was calculated by the Homeostasis Model Assessment Index of Insulin Resistance (HOMA-IR) form the following equation:

HOMA-IR =[Fasting insulin[mIULl])x(Fasting blood glucose[mmol/L])/22.5.

Assay of kidney markers

Preparation of kidney homogenate

The kidney homogenate was performed in a Teflon-glass homogenizer at 8°C. Ten milligrams were submerged in 2 mL of PBS containing 1 mM EDTA. Then, they were centrifuged at 18,000×g (-4°C) for 30 min. The supernatants were put in Eppendorf tubes, and preserved at -60°C till utilization.[17]

Assay of kidney oxidative stress markers

Malondialhyde (MDA) was determined by the method described,[17] using diagnostic kit of Randox (Randox Laboratories Ltd., UK). The activity of Glutathione S-Trasnferase (GST) was determined.The activity of Glutathione Peroxidase (GSH-Px) was determined by the method of.[18] The activities of catalase and SOD were determined using a commercially available kit (R&D System, Inc.).

Histological examination of kidney tissue

Part of the kidney tissue was kept in 10% formalin and embedded in wax to prepare microtome slices 10 mm thickness. Hematoxylin and Eosin dyes were used for examination of any pathological alterations.

Statistical Analysis

All data were expressed as Mean±S.D. The data was statistically analyzed using student tests. The *p*-value <0.05 was considered as statistically significant.

RESULTS

The phytochemical components identified by GC/MS of *Safawi* date extract showed that its high content of catechin, epicatchin, and procyanidins as the major flavonoids content abundant in the extract as shown in Figure 1.

Biochemical analysis are presented in Figures (2-11) revealed that, after four weeks of propylparaben exposure, there was a significant elevation in the levels of fasting blood glucose, HbA_{1c}, insulin, HOMA-IR, MDA, creatinine and reduction in the activities of GST, GS-Px, SOD, catalase(p<0.001) respectively compared with control.

Treatment with SDE (100 mg/kg/bw) significantly modulated the elevation of, glucose, HbA_{1c}, insulin, and MDA, and creatinine compared with untreated group. In addition, SDE enhanced antioxidants enzymes activities (GPx, GRase, SOD and catalase) while reduced MDA compared with untreated group (p<0.001).

Histopathological examination of kidney tissue supported the biochemical markers that showed the kidney acini in the peripheral part of kidney lobules of rats exposed to 100, 200 or 300 mg propylparaben after 4 weeks compared with control group Table 1. The kidney lobules were separated from each other with increased amount of connective tissue, there was mild increase in the amount of interlobular connective tissue. Notice the little exudates in the interlobular duct and mild congestion of blood vessels and mild increase in the amount of interlobular connective tissue and showed more inflammation and infiltration, nuclei are denser. After the fourth week, there was chronic inflammatory infiltration with chronic congestion of blood vessels. There was a high disruption in some acini in the peripheral part of kidney lobule.

Treatment with SDE improved the congestion of lobules, decreased inflammatory infiltration and integrity of the acini kidney cell.

DISCUSSION

The kidney, being highly susceptible to harmful external substances, has been linked to nephrotoxicity induced by arsenic toxicity in rat models. This association is characterized by elevated inflammatory, mitochondrial injury, and stress markers, as well as increased levels of urea and creatinine.[18] Given their widespread availability and ease of access, there is a growing interest in harnessing the medicinal potential of naturally occurring dietary components such as quercetin and ascorbic acid that possess anti-inflammatory and antioxidant properties, among other benefits.[19]

Propylparaben is inexpensive, antifungal and antibacterial used as preserving agent additive in cosmetics, pharmaceuticals, antimicrobial preservative, individually or in combination with other preservatives. The most commonly used methylparaben and propylparaben exert endocrine disrupting effect in animal model. These substances, which are taken via beverages or cosmetic products, are serious issues that need to be investigated for human and environmental health. Date was consumed in many countries for its high nutritional and medical purposes. It

Table 1: Histopathological changes in kidney tissue within 4 weeks.

	G	BS	Tubules			Interstitium	Cortico-medullary	Medulla
			Lining	Brush border	Lumen			
control	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Paraben(100 mg)	0	+	0	0	+	++	+	0
Paraben(200 mg)	++	+++	++	++	+	++	+	+
Paraben(300 mg)	+	+	+++	++++	+++	+++	++	+++
Paraben(300 mg)+SDE	+	+	+	+	+	+	+	+

Glomeruli (G), Bowman's spaces (BS).

was suggested that, date are a good source of natural antioxidants and used as a functional food in the control of oxidative stress. The beneficial of date use are a safe, natural alternative and complementary treatment.

This study investigated the protective effect of SDE against nephrotoxicity, oxidative stress and development of diabetes in rats exposed to propylparaben for four weeks. Rats exposed to propylparaben at dose 100 or 200 mg/kg b.w showed a non significant elevation of diabetic markers, lipid peroxidation, and decreased antioxidant enzymes. This is explained by ability of body to overcome this disturbance. Rats given propylparaben at dose 300 mg/kg b.w for 3 weeks showed the levels of fasting glucose, HbA_{1c}, insulin, c-peptide and HOMA-IR were significantly higher than control. This is in accordance with a study reported[19] paraben exert diabetogenic effect in experimental rats. It induces higher insulin secretion and insulin resistance as indicated by higher HOMA-IR values. In the current study, we found that, exposure of rats to propylparaben appears to significantly affected at dose 300 mg/kg bw by elevation of blood glucose, HbA_{1c}, insulin, c-peptide, MDA and antioxidant enzymes activities of kidney tissue. The elevation of these parameters may be due to accumulation of propylparaben in the body tissues that promote free radicals generation, release of insulin and increase insulin resistance. Treatment with SDE showed improvement of glycemic indices as compared with untreated rats. This is may be explained relative to flavonoids content of SDE (catechin, epicatechin and procyanidine) that modulate inflammatory mediators and inhibit oxidative stress to protect kidney tissue from damage and pancreatic β- cells from damage. This is in accordance with Amira *et al*,[20] who stated that treatment with aqueous extract *ajwa* and *Safawi* date seed significantly reduced the blood glucose

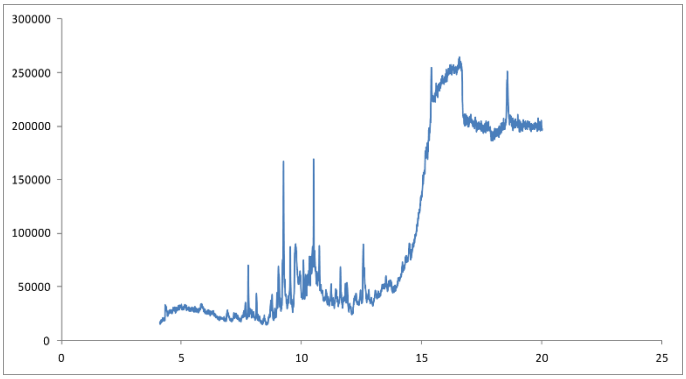

Figure 1: GC/MS chromatogram of major flavonoids from Safawi date extract.

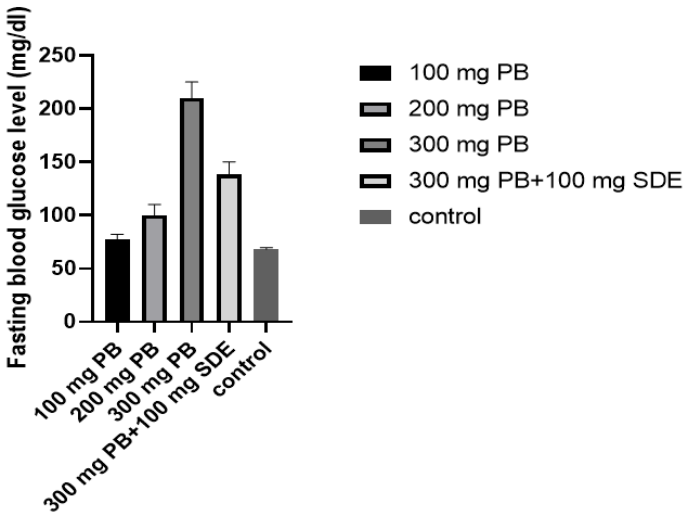

Figure 2: Fasting blood glucose level In all studied groups.

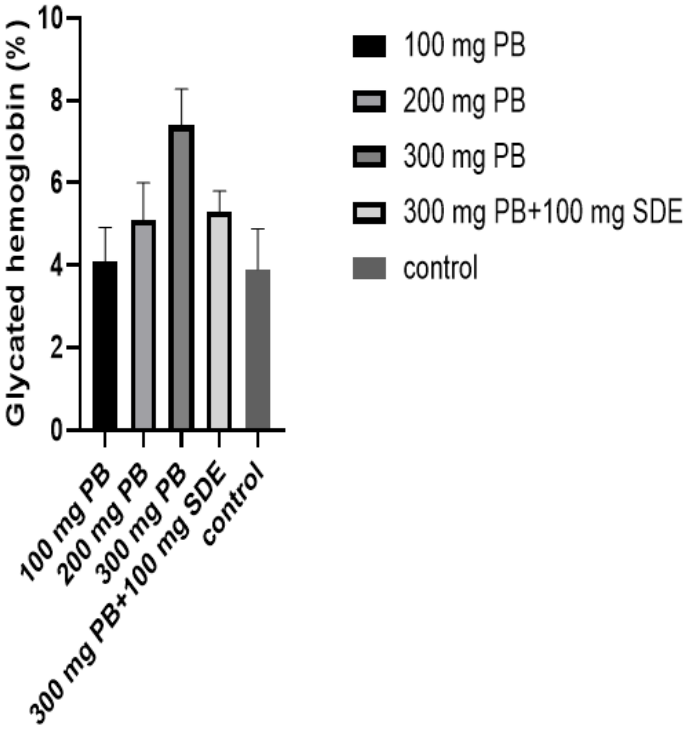

Figure 3: Glycated hemoglobin % in all studied groups.

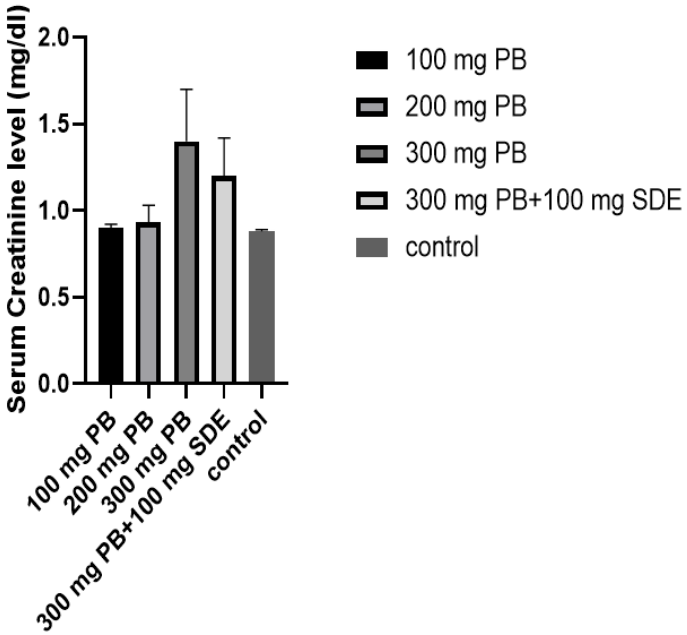

Figure 4: Serum creatinine level in all studied groups..

concentration in diabetic rats. Moreover, it also reflects better glycemic control and insulin status. It was reported that, diabetic rats treated with DSE (50 mg/L) showed hypoglycemic effect.[21] SDE was considered as anti-hyperglycaemic effect unlike insulin and other synthetic drugs. Oxidative stress is imbalance of oxidant and antioxidant that contributed to the development of diabetes.[22] Reactive oxygen species (ROS) produced due to metabolism or pollution is scavenged by antioxidant enzymes.[23] Moreover, it induce changes in the tissue content and activity of the antioxidant enzymes.[22] In the current study, rats given propylparaben 300 mg/kg bw for 3weeks showed that serum MDA level were higher than those of other groups, this is due to increased free radical production and normalized the levels when treatment with SDE. Flavonoids content of SDE possess antioxidant and anti-inflammatory activities.[20] Previous studies using date fruit by Hamad *et al*[23] showed that it possessed potent antioxidant activity, due to their phenolic and flavonoid contents. However, the antioxidant activity was correlated with the concentration of antioxidant content. However, the activities of the antioxidant enzymes were increased through the maturation process. Another study using three premium quality date varieties (*Khalas, Sukkari, and Ajwa*) evaluated the antioxidant content of their water extract, the results of which showed high contents of total phenols especially in Ajwa, although Sukkari had the highest rutin concentration, whereas catechin was similar in *Sukkari and Ajwa*.[8]

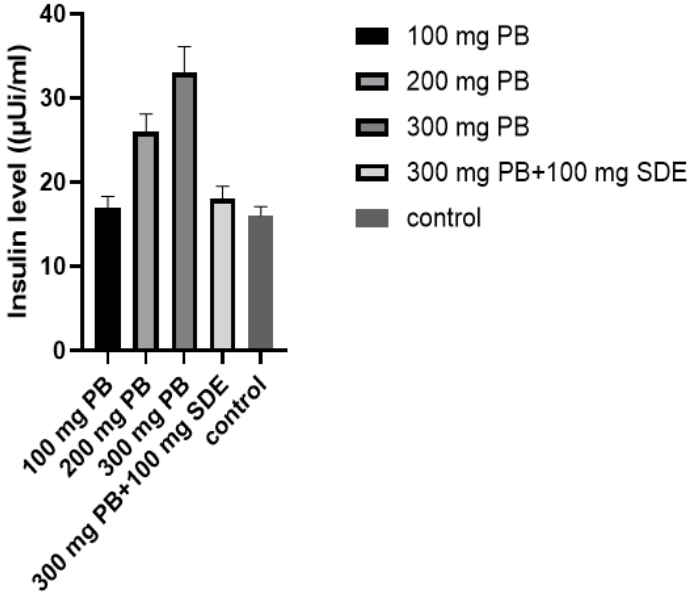

Figure 5: Insulin level in all studied groups.

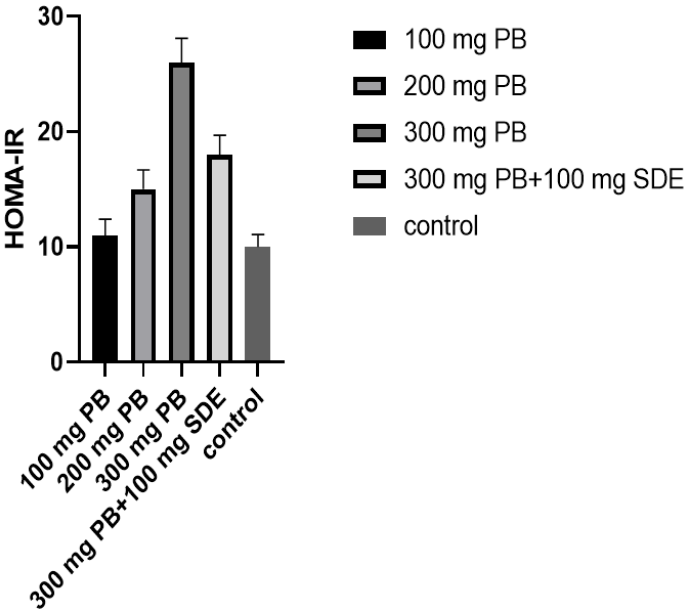

Figure 6: HOMA-IR in all studied groups.

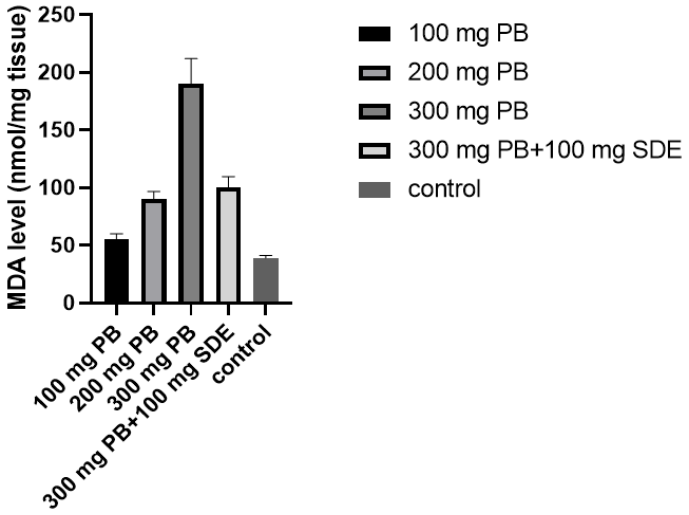

Figure 7: Malondiladhyde level in kidney tissue of all studied groups.

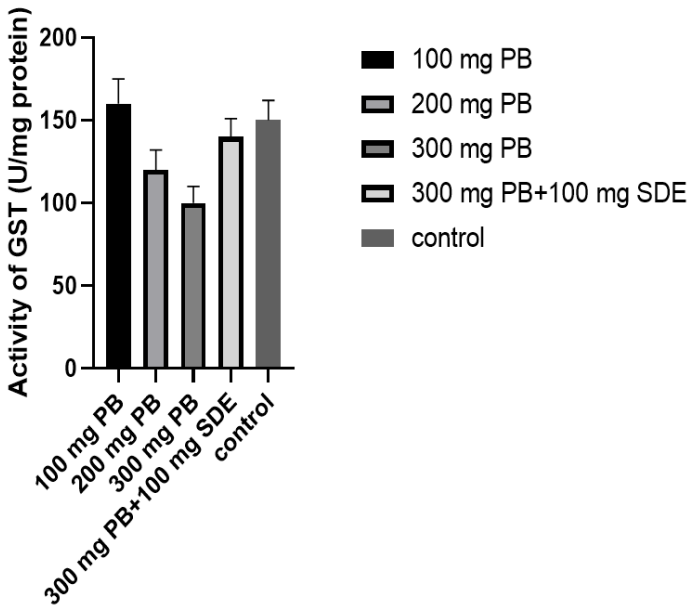

Figure 8: Activity of glutathione s-transferase in kidney tissue of all studied groups.

The beneficial effects of flavonoids on human health can be assessed in long-term studies related to management of different abnormalities. A range of chronic diseases, as diabetes, arthritis and atherosclerosis are most prevalent in elderly subjects. Indeed, it has been shown in a seven-country study that risk for cardiovascular diseases is significantly reduced in the aging population with increased consumption of flavonoid-rich diets, including the risk for stroke. In patients with coronary artery disease, polyphenol-rich diets reverses endothelial vasomotor dysfunction.

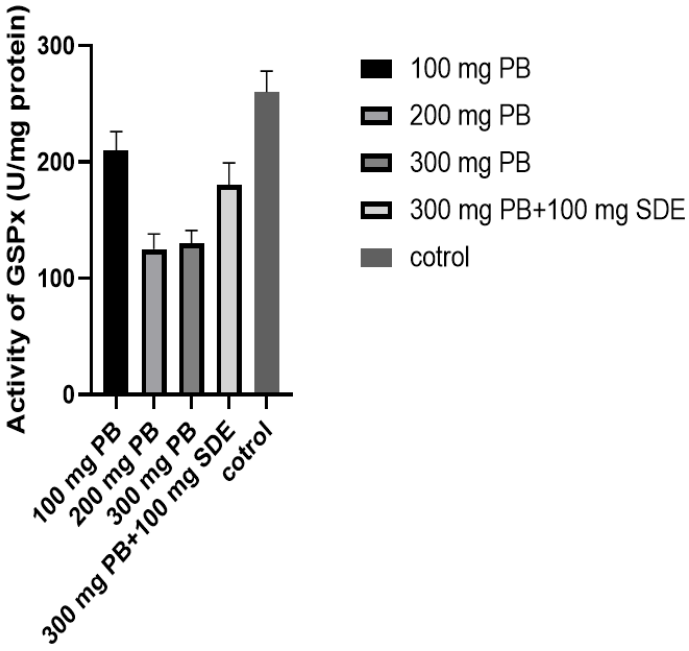

Figure 9: Activity of glutathione peroxidase in kidney tissue of all studied groups.

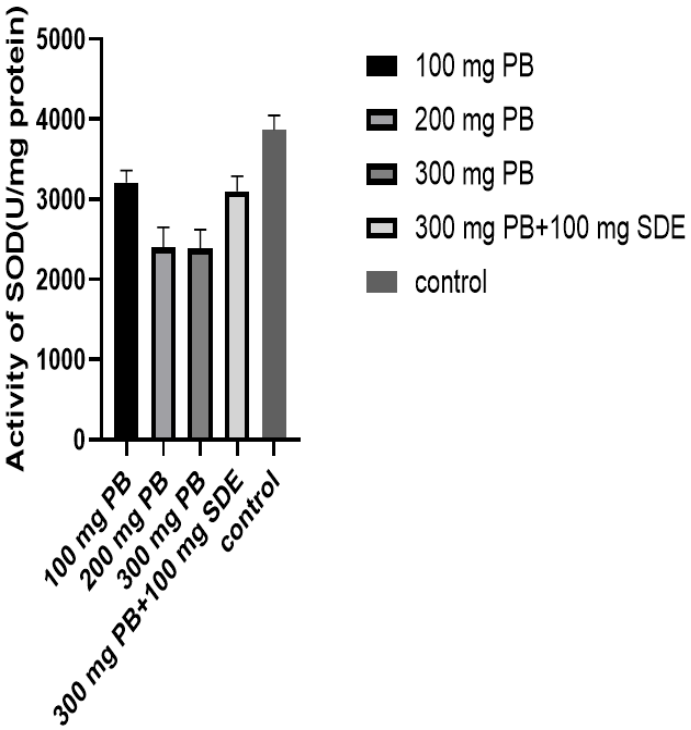

Figure 10: Activity of superoxide dismutase in kidney tissue of all studied groups.

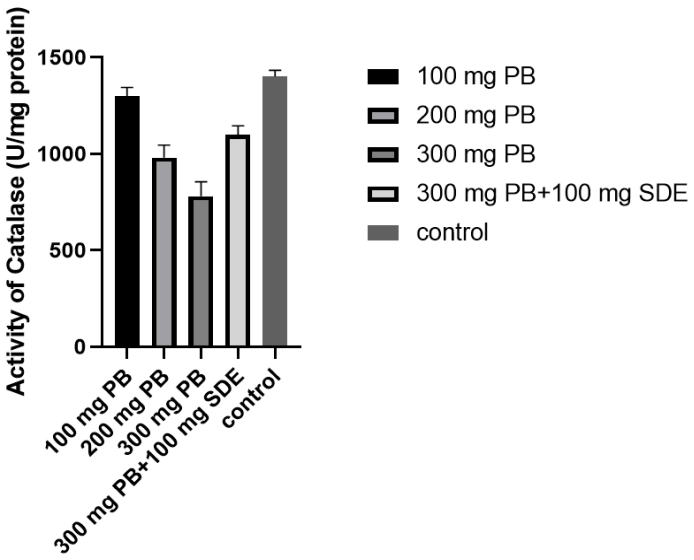

Figure 11: Activity of catalse in kidney tissue of all studied groups.

Elevated levels of fasting glucose and HbA_{1c} indicated abnormal secretion and efficacy of insulin due to inflammatory effect of propylparaben exposure. HMOA-IR is a marker of insulin resistance and pointed out that, hyper secretion of insulin in response to elevated blood sugar and abnormal action of insulin.

Release of inflammatory mediators as cytokine can induce β-cell dysfunction seems to be involved in the development of Type II diabetes. Data showed that, propylparaben at dose 300 mg for 3 weeks induce oxidative stress by increased MDA and reduced antioxidant capacity. These imbalance between oxidant and antioxidant may affect kidney function.

In *vivo* study, propylparaben administration mice was reported to be associated with an increase in lipid peroxidation in reactive oxygen species and free radical reactions, resulting in oxidative stress.[23,24, 25]

CONCLUSION

It was concluded that, higher doses exposure of propylparaben for three weeks was associated with increased insulin resistance and nephrotoxicity. Flavonoids of SDE increase insulin sensitivity and protect against diabetogensis. These results open a new window for further analysis to identify the signal mediated the associations of diabetic to possible reverse causation.

SUMMARY

Propylparaben caused increased oxidative stress by increasing MDA and reduction the antioxidant activities. The changes in redox status play a role in abnormality of the islets. The antioxidant enzymes activities were reduced in response to

propylparaben exposure after 3 weeks at a dose 300 mg/kg bw, this time was enough to caused abnormal islets morphogenesis. However, SDE normalize this abnormalities by enhancing its activity to scavenging free radicals produced.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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