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Research Paper

Rutin Protects Liver and Kidneys against the Toxicity of Plastic Compounds in Rats

Olufemi I. Oluranti [1*], Praise O. Akin-Aborishade [1], Atilola A. Olarinde [1], Babatunde A. Alabi [2], Esther O. Ojo-Ayangoke [1], Timilehin M. Mayowa [1], Marvelous O. Paseda [1], Ayomide V. Lawal [1], Ibukun M. Dahunsi [1]

[1] *Departments of 1Physiology, Bowen University, P.M.B. 284, Iwo, Nigeria*
[2] *Department of Pharmacology and Therapeutics, College of Health Sciences, Bowen University, P.M.B. 284, Iwo, Nigeria*

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*** Corresponding author:**
Olufemi I. Oluranti, Departments of 1Physiology, Bowen University, P.M.B. 284, Iwo, Nigeria. E-mail: olufemi.oluranti@bowen.edu.ng

ABSTRACT

Background: Environmental pollutants, such as plastic-derived substances Bisphenol-A and Di-butyl phthalate have been linked to an increase in the occurrence of human health hazards, including dysmetabolic syndrome, i.e., insulin resistance, and organ toxicity. In this syndrome, concurrent risk factors can give rise to cardiovascular disease, stroke, and type 2 diabetes. This study aimed to investigate the toxic effects of certain plastic compounds against kidneys and liver, and the potential protective role of rutin in rat. Rutin is a natural anti-inflammatory supplement that improves blood circulation and metabolic functions, lowers cholesterol and reduce arthritis pain.

Methods: Eighteen rats were divided randomly into three groups of six each and were treated for 28 days as follows: 1) Control (0.1% DMSO); 2) Bisphenol-A and Dibutyl phthalate, and 3) Bisphenol-A, Dibutyl phthalate and rutin. At the completion of the experimental period, the rats' hepatic and renal toxicity biomarkers, redox status and lipid profile were measured.

Results: Based the experimental findings, the toxicity of plastic substances increased in gamma-glutamyl transferase, urea, renal MDA and significant reductions in SOD and CAT activities, compared to those of the controls. The total plasma cholesterol and low-density lipoprotein (LDL) levels increased. The hepatic total cholesterol, LDL, FFA, TG levels increased. The HDL decreased while the total cholesterol, TG and LDL levels increased in the kidney. However, these biochemical alterations improved significantly by administering rutin supplement to the rats that were pretreated with the plastic compounds.

Conclusions: Flavonoid, rutin, demonstrated hepato-renal protective effect against the toxic effects of plastic compounds.

Keywords: Bisphenol A; Dibutyl Phthalate; Hepato-Renal Toxicity; Rutin

Introduction

Long-term exposure of live organisms and animals to bisphenol A and dibutyl phthalate has been associated with toxicity induced by these compounds [1]. The excessive usage and improper disposal of plastic products by humans have increasingly led to toxicity in a variety of animals and ecosystems [2]. It is well recognized that using plastic materials to store and preserve industrial goods and products exposes humans to the hazardous effects of bisphenol A and dibutyl phthalate [3]. Phthalates, which improve the flexibility and elasticity of plastics [4], are frequently found in consumer items, and are the primary components of plastics. Several factors have been associated with the plasticizers entry into containers, but prolonged storage of industrial products at high temperature and an extreme pH are the most crucial factors [5].

The increased rate of bisphenol A (BPA) and phthalate leakage into plastic materials have been linked to harmful health outcomes in humans, such as coronary artery disease [6], insulin resistance [7], and cancer [8-10]. Further, early female puberty, which is a risk factor for breast cancer, increased waist circumference, insulin resistance, shorter pregnancy duration, and low birth weight have all been associated with increased exposure to phtalates and bisphenol A [11]. The effects of phthalate on elevated systolic, diastolic, and mean arterial blood pressure have been reported by Jaimes, et al. [12]. Although the mechanism of toxicity of phthalate and BPA is not fully clear, a previous study [13] has revealed correlation between plasticizers and

oxidative stress, dyslipidemia, along with other abnormal conditions. These abnormalities were p38 mitogen-activated protein kinase (MAPK), extracellular signal regulated kinases 1 and 2 (ERK1/2), Akt, and nuclear factor-kappa-B (NF-kB) when phthalate was administered at varying doses to rats for 30 days [13].

Several studies have also confirmed the kidneys damage caused by DEHP [14-16]. At 52 weeks, DEHP exposure (1.2%; 3147 mg/kg/day) has led to renal tubular degeneration and decreased kidneys weight [14]. The down-regulation of PPARs has been identified as the molecular mechanism underlying DEHP's kidney toxicity [15]. Also, the use of phthalate-containing infusion systems for total parenteral nutrition has been linked to a 5.6-fold increased risk of cholestasis among neonatal infants at intensive care units, and the incidence of hepatobiliary dysfunction has changed from the initial 50% to final 13% after switching to phthalate-free tubing systems [16]. Despite the above information, there is a dearth of scientific data on the hepato-toxic effects of phthalate and BPA. In-depth research on the hepato-renal toxic effects of the co-exposure of BPA and phthalate is lacking. This is evident despite the known association between these compounds and human health conditions, such as cardiovascular disease, diabetes, reduced sperm quality, breast cancer, implantation failure, endometrial hyperplasia, and polycystic ovarian syndrome.

Health organizations have tried to reduce misuse and human dependence on plastics, but these efforts have not had much positive impact. This calls for additional research on the use of supplements as a safeguard against the harmful effects of long-term co-exposure to BPA and phthalate, particularly on vital organs, such as the liver and kidneys. Based on earlier studies [16, 17], rutin supplementation protects against the toxicity of BPA and phthalate. It reduces oxidative stress, inflammation, and the modulation of pro-apoptotic proteins, with a potential impact on PPAR and AMPK.

Aim of the Study: The current experimental study was conducted to investigate if rutin may protect against hepatic and renal damage induced by BPA and phthalate oxidative stress, and lipid dysfunction in a rat model.

Materials and Methods

Experimental Animals: Eighteen male Wistar rats weighing 150-180g were purchased from Iwo, Osun State, Nigeria. They were housed in the Bowen University's College of Health Science experimental animal facility. Over the duration of the experiment, the animals were maintained on the same dietary and environmental conditions, and at room temperature under 12-hour light/dark cycles. The rats were given a one-week acclimation period in the laboratory before starting the experiments. Also, they had free access to standardized food and clean potable water *ad libitum*.

Animal Grouping: In this study, the rats were randomly divided into three groups of six rats each as follows: Group 1(controls): Group 2: rats received dibutyl phthalate and bisphenol A (25mg/kg DBP + 25mg/kg BPA). Group 3: rats were orally given dibutyl phthalate, bisphenol A and rutin (Rt; 25mg/kg DBP + 25mg/kg BPA + 50mg/kg Rt). All treatments were administered to rats by oral gavage for 28 consecutive days. The doses of BPA, DBP and Rutin (Rt) were determined based on the data from a prior study [17].

Tissue and Blood Sampling: At the completion of the experiments, the rats were given pentobarbital sodium (50 mg/kg) intraperitoneally to make them unconscious. A cardiac puncture was made to obtain blood samples from each rat, which were then placed in heparinized bottles and left to stand for 30 minutes before being centrifuged at 3000 rpm for 5-min. The obtained plasma samples were frozen until used for further biochemical assays. The liver and kidneys were immediately removed, free of any adhering connective tissues, blotted, weighed, and the data recorded.

Biochemical Analyses: The plasma levels of uric acid, urea, and creatinine were determined by a standardized enzymatic colorimetric methods, using a Fortress diagnostics assay kit (Antrim, UK). Griess reagent was used to determine the nitric oxide level in the serum while the myeloperoxidase (MPO) enzyme level was determined by the method of Xia and Zweier [18]. The serum malondialdehyde (MDA) was determined using standardized, enzymatic, and colorimetric methods and test kits from Oxford Biomedical Research, Inc. (Oxford, MI, USA). Reduced glutathione (GSH), superoxide dismutase (SOD), catalase (CAT) alkaline phosphatase (ALP), aspartate transaminase (AST), alanine transferase (ALT), gamma-glutamyl transferase (GGT) and albumin were assayed by standard colorimetric methods, using reagents obtained from Randox Laboratory Ltd. (Antrim, UK). The plasma and tissue lipid profile were measured and estimated with a commercial assay kit and enzymatic colorimetric tests.

Statistical Analyses: The obtained data were represented as means ±standard error of the means (M ± SEM). One-way analysis of variance (ANOVA) was employed for data analyses, using GraphPad prism. For each variable, pairwise comparisons of the various groups were made via Newman-Keuls post hoc tests. The statistically significant differences were set at $P<0.05$.

Results

The derived experimental data were plotted in seven Figures; the descriptions of which are illustrated in Figures 1-7, and outlined below:

As shown in Figure 1, there was a significant increase in GGT in DBP + BPA exposed group when compared to the controls while no significant differences were found in the serum AST, ALT, ALP and albumin levels. However, supplementation with rutin was associated with a significant decline in the serum activities of AST and GGT.

Based on the data illustrated in Figure 2, the plasma urea significantly increased following DBP + BPA administration compared to the controls, creatinine increased by 29.41% while no significant differences was found in the uric acid levels. Administration of rutin reduced the urea and creatinine levels by 7.06% and 17.05%, respectively, compared to the DBP + BPA group.

As presented in Figure 3, there was a decrease in the catalase activity (14.56%), and increases in both nitric oxide (21.09%) and MPO (69.83%) in the plasticizer group compared to those of the controls while rutin administration reversed these observed changes.

As demonstrated in Figure 4, after the oral administration of DBP + BPA to the rats, the renal MDA level significantly increased concurrently with a significant reduction in the SOD and CAT activities compared to those of the controls. This effect was reversed by supplementing rutin to the rats treated with plasticizers, where a significant reduction in the MDA level was observed together with increases in the serum levels of SOD and CAT.

The data in Figure 5 indicate that there were increases in the total cholesterol and low-density lipoprotein (LDL), and the plasma levels of DBP + BPA in the treated rats compared to those of the controls. However, rutin administration restored the TC and LDL levels in the rats' plasma.

As seen in Figure 6, there was significant increases in the liver total cholesterol, LDL, FFA, TG levels and a decrease in HDL compared to those of the control after administering DBP + BPA to the rats. Interestingly, the oral administration of rutin supplement restored the lipid profile to near the normal control levels.

Finally, as shown in Figure 7, in the plasticizer group, there were increases in the total cholesterol, TG and LDL levels in the kidneys compared to those of the controls. Supplementation with rutin significantly reduced the TC, TG and LDL levels in the group pretreated with DBP + BPA + rutin compared to the rats that received DBP + BPA only.

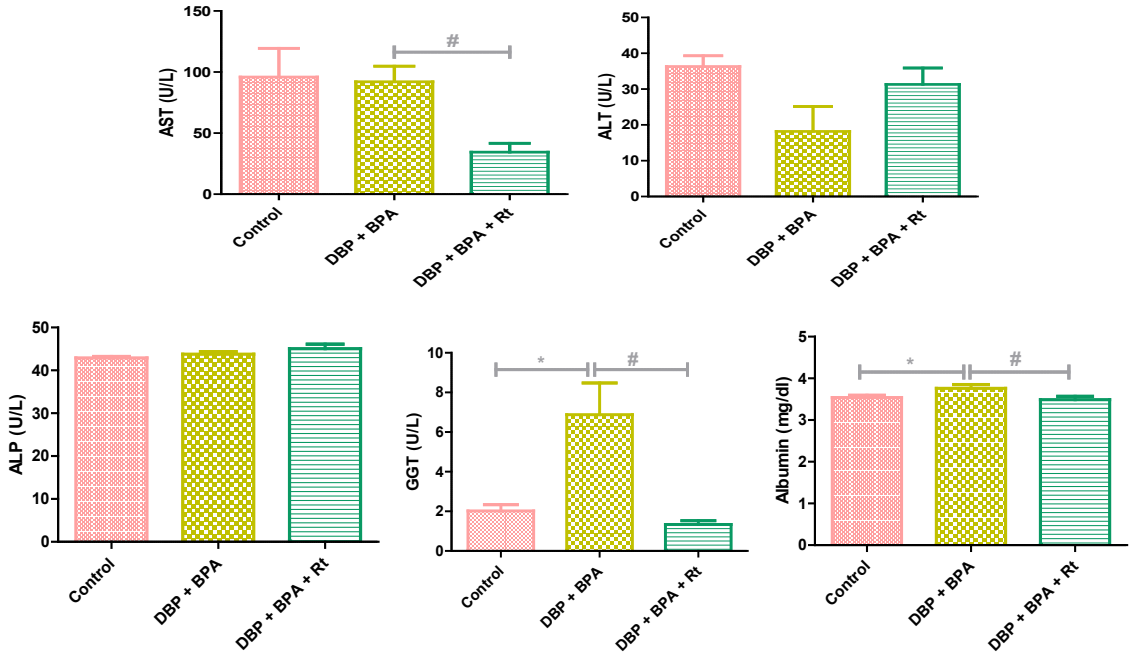

Figure 1. The effect of DBP, BPA and rutin on the rat liver.

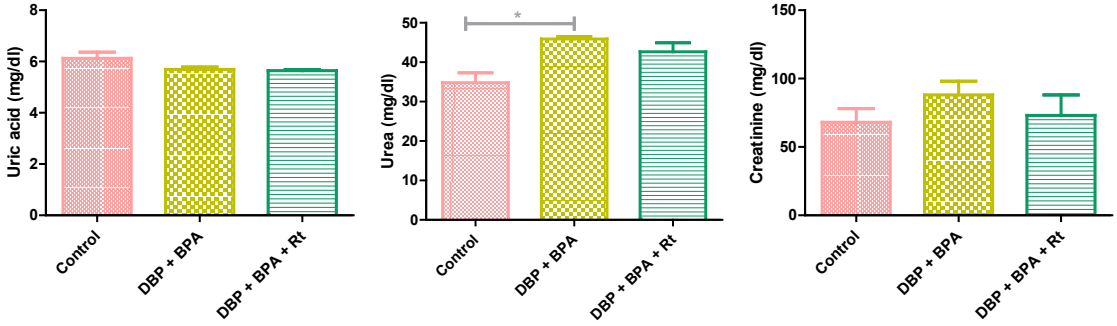

Figure 2. The effect of DBP, BPA and rutin on the rat kidneys.

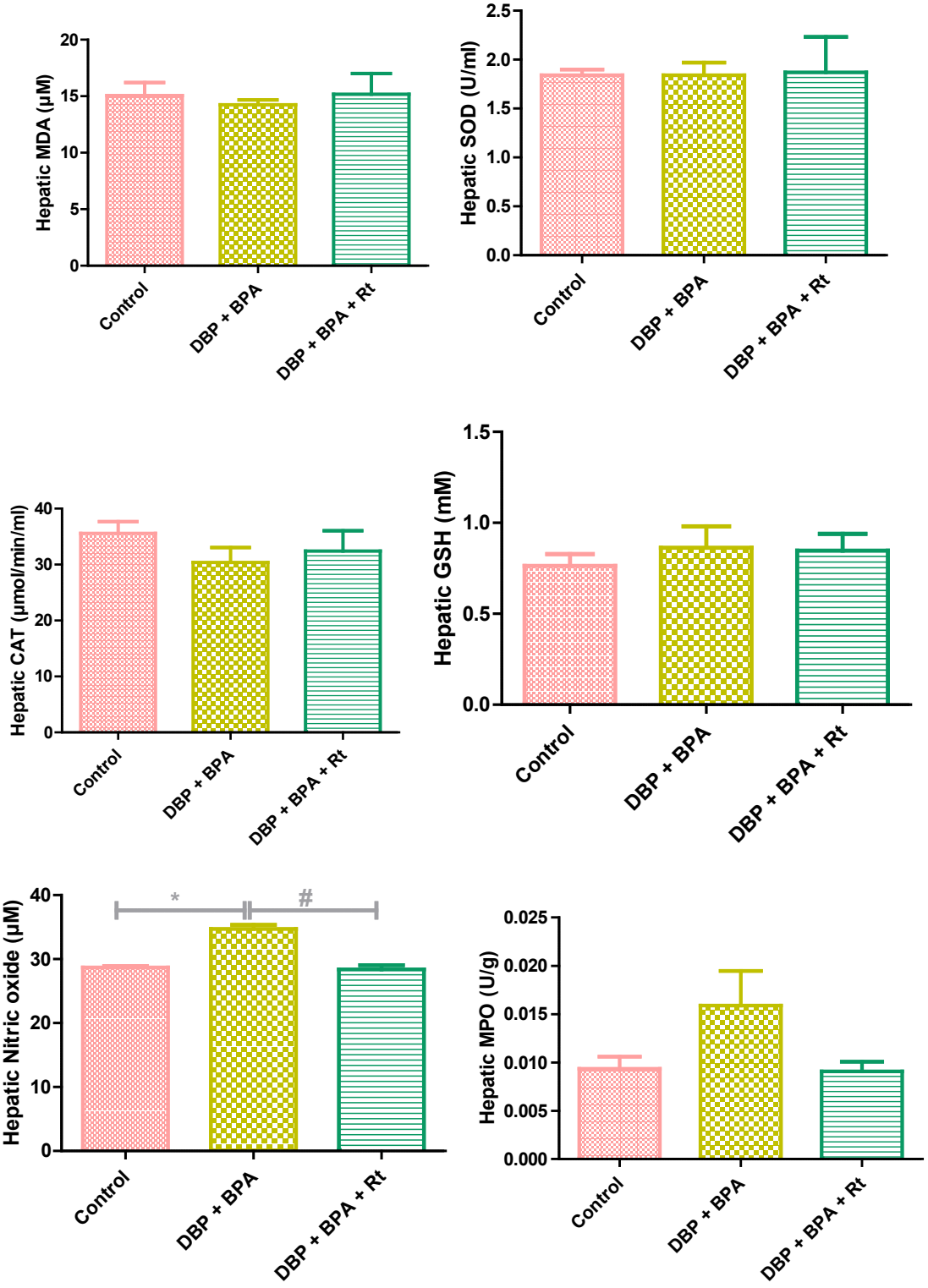

Figure 3. The effect of DBP, BPA and rutin on the rat hepatic redox status.

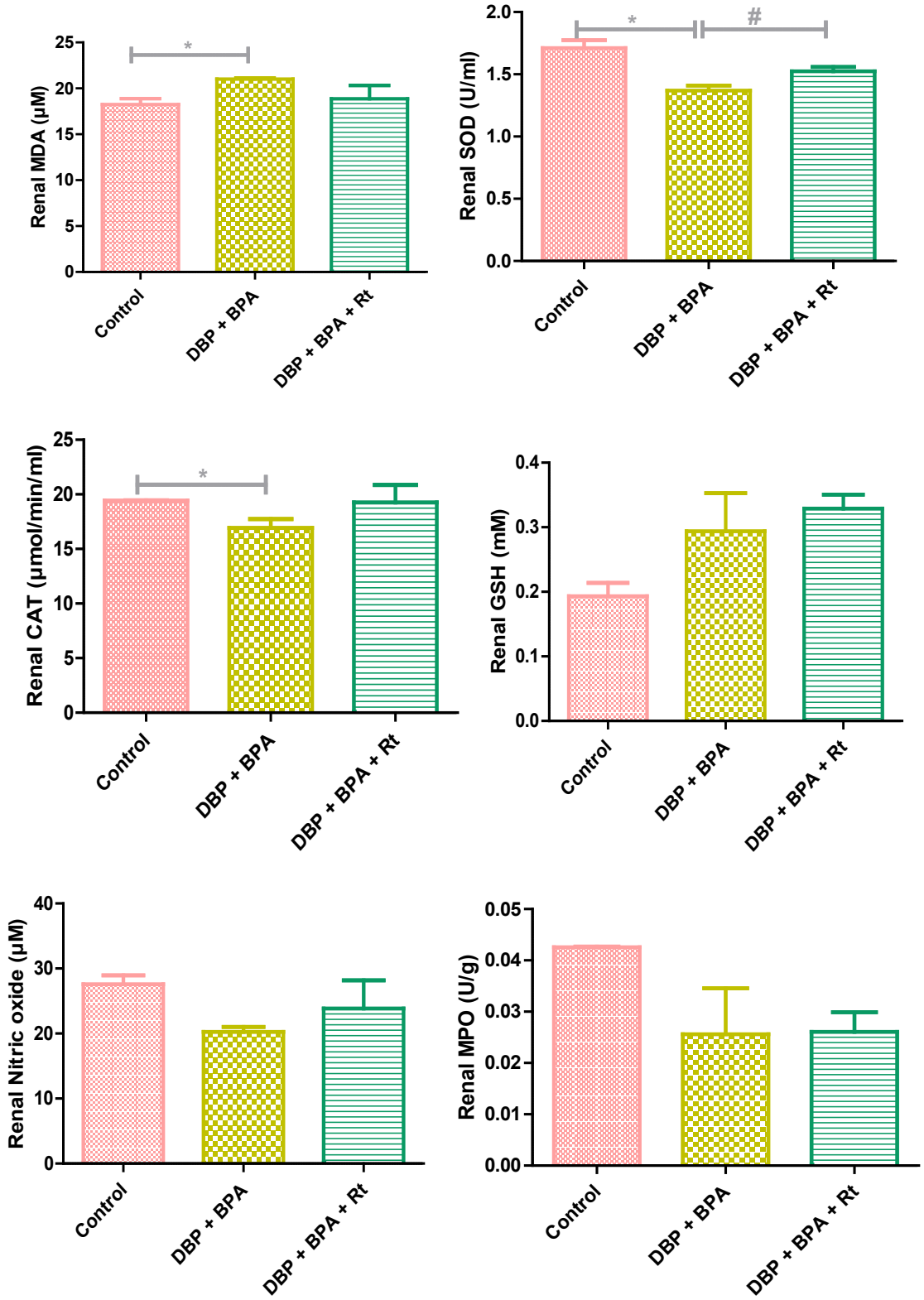

Figure 4. The effect of DBP, BPA and rutin on the rat renal redox status.

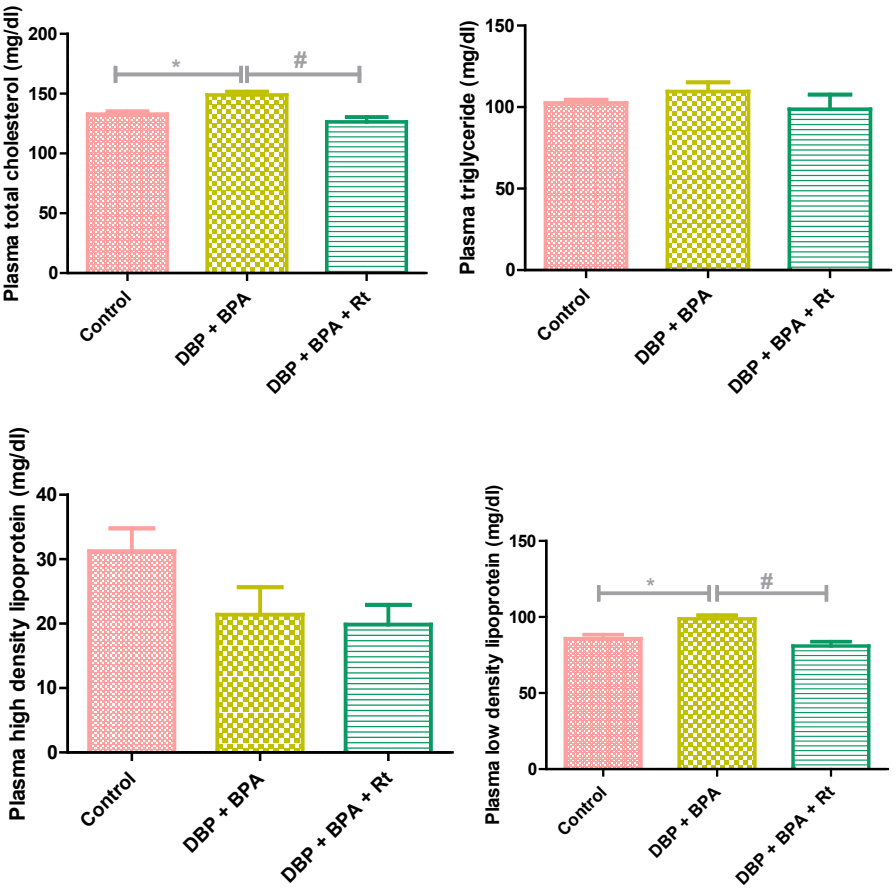

Figure 5. The effect of DBP, BPA and rutin on rat plasma lipid profile.

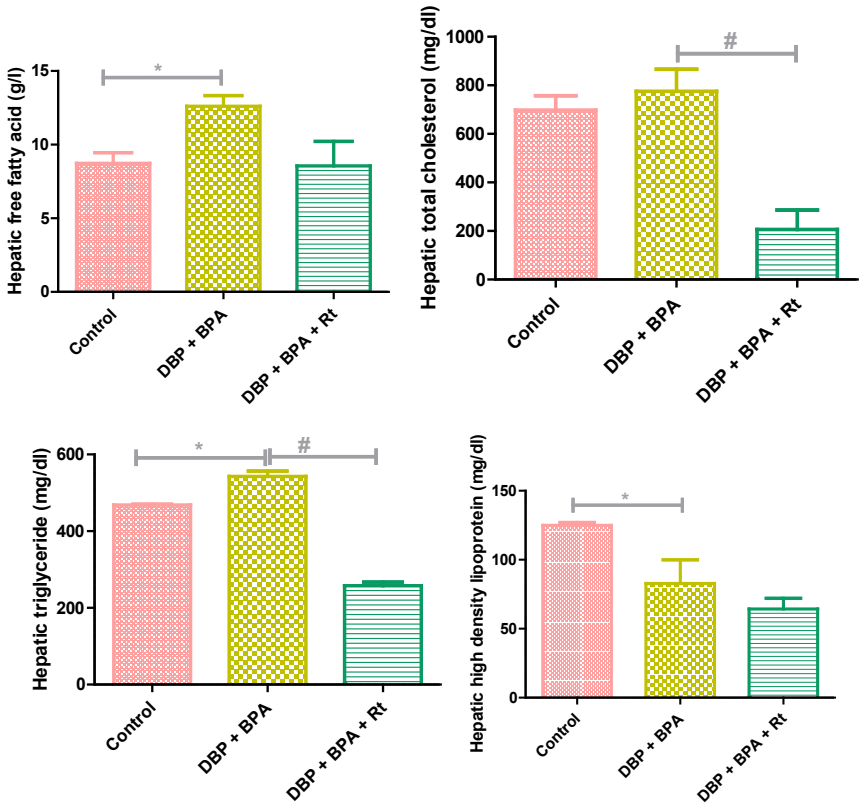

Figure 6. The effect of DBP, BPA and rutin on the rat hepatic lipid profile.

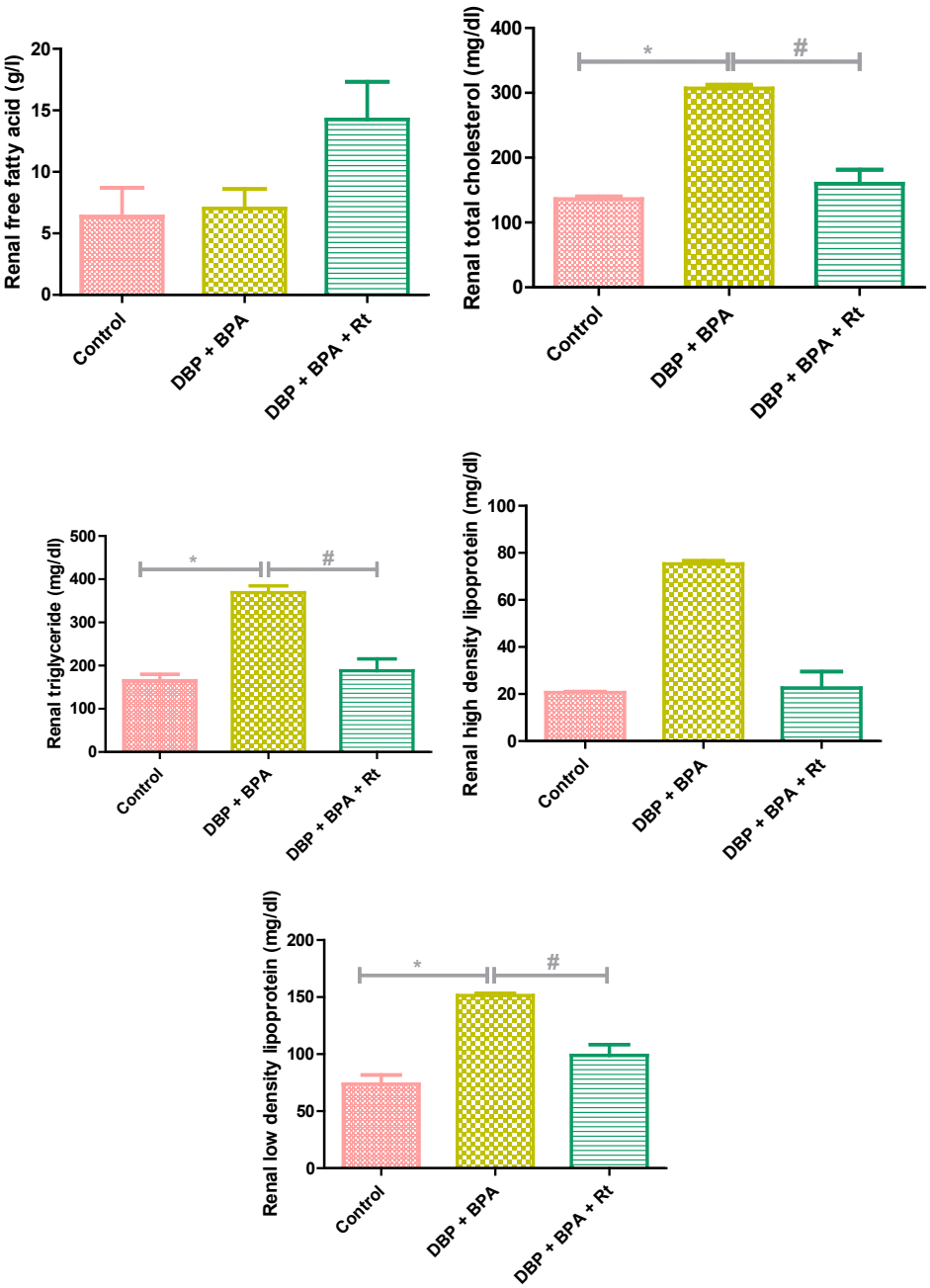

Figure 7. The effect of DBP, BPA and rutin on the rat renal lipid profile.

Discussion

Considering the widespread applications of plastic materials as parts of consumer and industrial goods, human exposure to these materials is essentially unavoidable [19]. Therefore, the goal of the current experimental study was to determine whether rutin consumption may lower the sub-acute toxic effects of combined dibutyl phthalate (DBP) and bisphenol A (BPA).

Considering our validated results, plasticizers had negative impact on the rats' liver as evident by marked elevation of the liver enzymes in the plasma. The elevations in the liver enzymes may be explained by altered hepatocytes' membrane permeability induced by plasticizers. As a result, the cell membrane loses its functional integrity and the enzymes leak out into the blood. This interpretation is in agreement with the findings reported by earlier studies [20-22]. Interestingly, the toxic effects of the plasticizers were reversed upon using rutin, which brought the serum levels close to those of the controls. The findings were consistent with those reported by Khan, et al. [23] and Reddy, et al. [24] in male rat models for the liver damage.

Due to its polyphenolic nature, rutin acts as a membrane-stabilizing agent, preventing enzyme leakage and preserving the homeostasis of liver enzymes [25]. Rutin has the capacity to quench singlet oxygens and eliminate peroxyl radicals with profound positive impacts on the functional integrity

of the liver, which may be linked to its consolidating action [26, 27]. Administering plasticizers cause nephrotoxicity as evident by the elevations of plasma urea and creatinine levels. High serum urea and creatinine levels are indicators of severe damage to the structural integrity of nephrons [28]. The co-administration of rutin significantly reduced the levels of these diagnostic markers. Previous studies have reported that rutin can modulate nephrotoxicity through its regulatory effect on apoptotic pathways, including the inhibition of caspases [29, 30].

The term "oxidative stress" defines a change in the cellular redox equilibrium. Our findings showed that exposure to plasticizers significantly increased the lipid peroxidation marker (MDA) and considerably lowered the SOD and CAT enzymes in the rats' liver and kidneys. According to previous reports [31, 32], BPA causes oxidative stress in the brain, kidneys, testicles, pancreas, and liver. The injection of 50 mg/kg BPA has raised NO and TBARS levels while decreasing GSH, SOD, and CAT levels in rats' liver tissue [31]. Further, BPA injection reduces SOD, GSH, and CAT activities and raises the MDA level in male rats' pancreatic tissue [32]. By oxidizing tissues' hydrogen peroxide, CAT protects tissues from hydroxyl radicals. By converting hydrogen peroxide into hydrogen oxide, it also serves as an antioxidant enzyme that lowers or inhibits the overproduction of hydrogen peroxide [33]. The significant reduction in the activity of this enzyme, as documented in the current study, could be due to exposure to plasticizers and its inhibition as a result of elevated reactive oxygen species (ROS) in mitochondria and microsomes. Further, treatment with rutin significantly decreased the MDA but increased the SOD and CAT activities. Rutin acts as a scavenger of ROS by donating hydrogen atoms to superoxide anions, hydroxyl and peroxyl radicals [34]. By the activation of Nrf2 and repression of iNOS, it also functions as a master redox switch [17, 35].

One of the main risk factors for cardiovascular disease is dyslipidemia. Considering the current study's findings, there were higher levels of total cholesterol and low-density lipoprotein (LDL) in the plasma, liver, and kidneys of the rat group treated with plasticizers compared to those of the control group. Moreover, there was a considerable rise in triglyceride levels in the rats' liver and kidneys, a rise in free fatty acid (FFA) and a decrease in the high-density lipoprotein (HDL) levels in the liver. Curiously, rutin was able to restore the lipid profile to a level that was quite close to the controls. Also, rutin improved the TC and LDL levels in plasma, the liver, and the kidneys; improved the TG levels in the liver and kidneys; and improved the FFA levels in the liver. This is consistent with the findings reported by a number of earlier studies [17, 22, 36-39].

It has been noted that BPA exposure alters the composition of fatty acids, increases hypertriglyceridemia and hypercholesterolemia, and upregulates genes linked to de novo lipogenesis and cholesterol synthesis in rat liver [40]. Platicizers may induce sterol regulatory element binding protein-1, a transcription factor, to express more often, and by increasing the amount and activity of the enzymes that catalyse lipogenesis and cause fatty liver [36]. By having an antagonistic impact on the nuclear receptor known as peroxisome proliferator-activated receptor (PPAR)-α and preventing its activity, plasticizers may play a role in the development of dyslipidemia by disrupting the metabolism and elevating lipid levels [33].

Rutin appears to dramatically lower TC, TG, HDL, and LDL, and there is an inverse relationship between flavonoid intake and total plasma cholesterol concentrations [41]. Rutin's ability to reduce lipid levels has been supported by numerous studies [42-44]. By changing the genes expression linked to lipid metabolism, rutin may enhance the plasma and tissue lipid profile. Also, TG levels are decreased by boosting the liver gene expression linked to lipid metabolism and decreasing the expression of PPAR-α. Moreover, it can lower the expression of the sterol regulatory element-binding protein 1 (SREBP-1) target gene, glycerol-3-phosphate acyl transferase 1, mitochondrial (Gpam), which is essential for the production of triglycerides [45].

Conclusions

Considering the current study findings, it can be established that rutin treatment in the animal model resulted in significant hepato-renal protection against the tissue toxicities induced by plasticizers. Therefore, rutin has the ability to protect kidneys and liver against plasticizers toxicity by the improved presentation of toxicity biomarkers, redox status and lipid profile. Therefore, this study demonstrated that the flavonoid rutin could be applied for mitigation against environmental and health hazards, particularly plastic-related compounds.

Conflicts of Interest

The authors declare that there is no known conflict of interest.

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Ethical Guidelines

All experimental guidelines were approved by the Bowen University Ethical Review Committee with the reference number BUREC/07i/20 by following the rules of the National Institutes of Health Guide for the Treatment and Use of Laboratory Animals.

Authors' Contributions

OIO; Concept, design, manuscript preparation, editing and review; POA, AAO, EOO, TMM, MOP, AVL, IMD; experimental studies, data analysis, statistical analysis; BAA; data analysis, manuscript preparation

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