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Protective Activity of Glutamine against Bisphenol A-induced Nephrotoxicity in Rats

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Abstract

Background: Bisphenol A (BPA) can impair kidney function via oxidative stress. Glutamine (Gln) is an amino acid with antioxidant and immunomodulatory activities. This study assessed the protective activity of Gln against BPA-induced nephrotoxicity in rats

Methods: Thirty adult male Wistar rats (200-230g) were randomly divided into 6 groups (each containing 5 rats). The rats were orally treated daily for 60 days as follows: Groups A (Control), B, and C were treated with normal saline (0.2 mL), Gln (80 mg/kg), and BPA (50 mg/kg), respectively. Groups D-F were supplemented with 20 mg/kg, 40 mg/kg, and 80 mg/kg of Gln before treatment with BPA (50 mg/kg), respectively. Blood samples were collected and serum renal biochemical markers were measured. The kidneys were weighed and evaluated for oxidative stress markers and histological changes.

Results: The administration of BPA decreased body weight ($p<0.01$) and increased kidney weight ($p<0.01$) when compared with the control group. The BPA-induced alterations in serum renal biochemical markers were accompanied by elevated urea ($p<0.001$), creatinine ($p<0.001$), and uric acid levels ($p<0.001$) as well as decreased electrolytes ($p<0.01$) when compared with the control group. Altered kidney oxidative stress markers caused by BPA were marked by a significant decrease in glutathione, catalase, superoxide dismutase, and glutathione peroxidase levels ($p<0.001$) with a significant increase in malondialdehyde levels ($p<0.001$) when compared with the control group. Moreover, BPA caused kidney tubular necrosis, widened bowman's space, collapsed glomerulus, and lipid accumulation. However, supplementation with Gln (20, 40, and 80 mg/kg) significantly reversed the BPA-induced nephrotoxicity in a dose-dependent manner when compared with the BPA group. Furthermore, different doses of Gln restored kidney histology.

Conclusion: Based on the results, Gln may have clinical protective effect against BPA-associated nephrotoxicity.

Highlights:
BPA treatment induced nephrotoxicity and oxidative stress in rats
Different doses of Glutamine reversed Bisphenol A-induced nephrotoxicity
The protective effect of Glutamine against Bisphenol A- induced nephrotoxicity was dose-dependent.

Introduction

Bisphenol A (BPA) is an essential component used for the production of epoxy resins, polycarbonate plastics, and hard plastic bottles that have everyday applications. Epoxy resins are used as coatings for food packages, polyvinyl chloride pipes, and automobile components (1). The frequent use of BPA-associated products has led to measurable BPA levels in various human biological fluids, including neonatal blood, amniotic fluid, and human breast milk (2). It has also been found in the blood and urine samples of humans (3). Exposure to BPA may lead to accumulation, thereby incapacitating the activities of vital organs, including the kidneys. Moreover, elevated levels of BPA have been reported in people with renal diseases, which is characterized by decreased glomeruli filtration rate (4,5). Several experimental studies correlated BPA accumulation, its plasma levels with impaired renal function (6). The exposure of animals to BPA causes deleterious effects on kidney function in various capacities, such as increased expression of proinflammatory mediators, the induction of oxidative stress, and the incapacitation of antioxidants response in renal tissues (5). BPA can increase the expression and enzyme activity of caspase-3 in renal tissues, which can lead to cell apoptosis (7). This has been associated with azotemia indicated by increased blood urea nitrogen and serum creatinine concentrations (8). Experimental studies have shown impaired kidney morphology characterized by glomerular atrophy, intratubular hemorrhage, and tubular necrosis (9).

Glutamine (Gln) is an essential L-α-amino acid with many metabolic functions, including gluconeogenesis, acid-base balance, homeostasis, nitrogen transport proteins, and nucleic acids syntheses. It plays an important role in cell homeostasis and organ metabolism (10, 11). This amino acid is also essential for nucleotide and glutathione (GSH) syntheses, which contribute to the reduction of oxidative stress (12). In GSH biosynthesis, Gln supplies glutamate to the GSH system, which is a primary source of cellular antioxidant defense (12). It can protect cells and tissues from stress and injuries by decreasing inflammation and oxidative stress and improving immune cell function (10). Studies have reported that Gln decreased renal injury caused by acetaminophen (13) and diabetes-induced nephropathy (14). It attenuates cisplatin-induced renal injury and inhibits renal cell apoptosis (15). Given the important protective functions of Gln in renal injury, this study aimed to assess the protective activity of Gln against PBA-induced renal injury.

Methods

Animals and chemicals

Thirty adult male Wistar rats (200-230 g) were randomly divided into 6 groups (A-F), each containing 5 rats. The rats were maintained in a 12/12-h light/dark cycle under natural conditions, in plastic cages. Rat chow and water were supplied to the rats' *ad libitum*. The rats were handled according to the Guide for the Use of Laboratory Animals (16). The rats were obtained from the animal unit of the Faculty of Pharmacy, Madonna University, Rivers State, Nigeria. Bisphenol A (Loba Chemie Pvt. Ltd, India) and L-Glutamine (Qualikems Fine Chem Pvt Ltd, India) were purchased. Approval was obtained from the Research Ethics Committee of the Department of Pharmacology, Faculty of Pharmacy, Madonna University (Approval code: REC/PHARM/013/2022).

Animal treatment

The rats were orally treated daily for 60 days as follows: Groups A (Control), B, and C were treated with normal saline (0.2 mL), Gln (80 mg/kg) (17), and BPA (50 mg/kg) (18), respectively. Groups D-F were supplemented with 20 mg/kg, 40 mg/kg, and 80 mg/kg of Gln before treatment with BPA (50 mg/kg), respectively.

Animal sacrifice and evaluations of serum biochemical markers

After the treatment, the rats were weighed and anesthetized. Blood and kidney samples were obtained for biochemical assessments and oxidative stress marker assay, respectively. Kidney samples were also assessed for histological changes. Blood samples were centrifuged at 1,500 RPM for 15 minutes, and sera were extracted and evaluated for serum total protein, urea, albumin, uric acid,

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potassium, bicarbonate, chloride, and sodium using an auto analyzer (Konelab™ PRIME 60i, Thermo Scientific, Vantaa, Finland).

Determination of relative kidney weight

The relative kidney weight was calculated according to the following formula:

$$\text{Relative kidney weight} = \frac{\text{Absolute kidney weight (gram)} \times 100}{\text{Body weight (gram)}}$$

Evaluation of kidney oxidative stress markers

Kidney superoxide dismutase (SOD) was measured according to a previous study (19). Malondialdehyde (MDA) was estimated as explained by Buege and Aust (20). Moreover, GSH was estimated according to the method explained by Sedlak and Lindsay (21). Glutathione peroxidase (GPx) was determined according to the protocol explained by Rotruck et al. (22). Catalase (CAT) was estimated as described by Aebi (23).

Histological assessment of the kidney

Kidney tissues were obtained and kept in 10% formalin saline. After 24 hours, the kidney tissues were dehydrated in graded solutions of alcohol. Kidney tissues were processed, embedded in paraffin wax, and sectioned (with 3 µm thickness) using a microtome. The sectioned tissues were placed on slides and then stained with Haematoxylin and Eosin (Bio Lab Diagnostics Limited, Mumbai, India). The slides were later examined under a light microscope.

Statistical analysis

Data were presented as mean ± standard error of the mean (SEM). Data were analyzed using one-way analysis of variance (ANOVA) and Bonferonni post hoc test using GraphPad Prism 5 (San Diego, CA USA). The statistical significance level was set at 0.05, 0.01 and 0.001

Results

Effects of Gln on the body and kidney weights of rats treated with BPA

The body and kidney weights of Gln (80 mg/kg)-administered rats did not change significantly when compared with the control. The administration of BPA significantly decreased body weight ($p< 0.01$) and significantly increased kidney weight ($p<0.01$) when compared with the control. However, the body and kidney weights were restored after Gln (20 mg/kg, 40 mg/kg, and 80 mg/kg) supplementation when compared with the BPA group (Table 1).

Table 1: Effect of Gln on body and kidney weights of rats treated with BPA

Dose (mg/kg)	Final body weight (g)	Absolute kidney weight (g)	Relative kidney weight (%)
Control group	265.8±18.0	0.77±0.04	0.29±0.08
Gln 80	265.7±16.9	0.70±0.06	0.26±0.01
BPA 50	180.3±11.0 [a]	2.00±0.05 [a]	1.11±0.07 [a]
Gln 20+ BPA50	220.4±16.7 [b]	1.51±0.07 [b]	0.69±0.09 [b]
Gln 40+ BPA50	261.7±14.4 [c]	1.00±0.09 [c]	0.38±0.03 [c]
Gln 80+ BPA50	262.5±16.7 [c]	0.80±0.04 [c]	0.30±0.05 [c]

BPA: Bisphenol A, Gln: Glutamine

[a] Significant difference when compared with the control group ($p<0.01$).

[b] ($p<0.05$) and [c] ($p<0.01$) significant differences when compared with the BPA group.

Effects of serum Gln on renal function markers and electrolytes of rats treated with BPA

The administration of Gln (80 mg/kg) had no significant effect on serum urea, creatinine, uric acid, and electrolytes (Tables 2 and 3). However, BPA administration significantly increased serum urea, creatinine, and uric acid levels ($p<0.001$) and significantly decreased serum electrolytes ($p<0.001$) when compared with the control. In addition, Gln (20 mg/kg, 40 mg/kg, and 80 mg/kg) supplementation significantly decreased serum urea, creatinine, and uric acid levels in a dose-dependent manner. Serum electrolytes increased significantly in the Gln (20 mg/kg, 40 mg/kg, and 80 mg/kg) supplemented rats when compared with the BPA group (Tables 2 and 3).

Table 2: Effect of Gln on serum biochemical parameters of rats treated with BPA

Dose (mg/kg)	Creatinine (mmol/L)	Urea (mmol/L)	Uric acid (mmol/L)
Control group	115.8±2.60	5.26±0.23	1.75±0.65
Gln 80	110.5±10.4	3.10±0.20	1.79.±0.01
BPA 50	272.6±14.3[a]	15.5±0.31 [a]	4.70±0.06 [a]
Gln 20 + BPA 50	220.3±16.6[b]	11.7±0.13 [b]	4.01±0.13 [b]
Gln 40+ BPA 50	171.7±13.3[c]	8.23±0.75 [c]	3.25±0.24 [c]
Gln 80+ BPA 50	130.0±10.7[d]	5.65±0.45 [d]	1.90±0.50 [d]

BPA: Bisphenol A, Gln: Glutamine

[a] ($p<0.001$) Significant difference when compared with the control group.

[b] ($p<0.05$) [c] ($p<0.01$) [d] ($p <0.001$) Significant difference when compared with the BPA group.

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Table 3: Effect of Gln on serum electrolytes of rats treated with BPA

Dose (mg/kg)	Potassium (mmol/L)	Sodium (mmol/L)	Chloride (mmol/L)	Bicarbonate (mmol/L)
Control group	6.07±0.28	122.53±13.4	100.72±9.01	22.45±2.53
Gln 80	6.10±0.37	120.02±10.2	110.53±8.11	23.05±2.09
BPA 50	2.70±0.32 [a]	60.51±9.03 [a]	44.87±5.76 [a]	12.53±1.76 [a]
Gln 20 + BPA 50	3.34±0.65 [b]	81.36±6.9 [b]	56.54±5.05 [b]	15.86±1.05 [b]
Gln 40+ BPA 50	4.42±0.15 [c]	101.70±10.5 [c]	77.06±5.70 [c]	19.32±1.70 [c]
Gln 80+ BPA 50	5.89±0.60 [d]	122.94±12.1 [d]	99.75±7.64 [d]	21.50±3.64 [d]

BPA: Bisphenol A, Gln: Glutamine

[a] ($p<0.001$) Significant difference when compared with the control group.

[b] ($p<0.05$) [c] ($p<0.01$) [d] ($p <0.001$) Significant difference when compared with the BPA group.

Effect of Gln on kidney oxidative stress parameters of rats treated with BPA

The administration of Gln (80 mg/kg) had no significant impact on kidney antioxidants (SOD, GSH, CAT, and GPx) and MDA levels when compared with the control group. In contrast, BPA administration significantly decreased kidney antioxidants ($p < 0.001$) and significantly increased MDA levels ($p<0.001$) when compared with the control group (Table 4). Supplementation with Gln (20 mg/kg, 40 mg/kg, and 80 mg/kg) significantly increased kidney antioxidants and significantly decreased kidney MDA levels in a dose-dependent manner when compared with the BPA group (Table 4).

Table 4: Effect of Gln on oxidative stress parameters of rats treated with BPA

Dose mg/kg	MDA (nmol/mg protein)	GSH (µmole/mg protein)	CAT (U/mg protein)	GPx (U/mg protein)	SOD (U/mg protein)
Control group	0.45±0.07	10.82±0.79	25.84±2.32	19.03±1.11	26.84±3.24
Gln 80	0.40±0.05	10.93±0.98	26.03±2.17	19.71±2.59	27.01±2.00
BPA 50	1.61±0.09[a]	4.05±0.16[a]	7.56±0.38[a]	7.00±0.81[a]	9.32±0.06[a]
Gln 20+ BPA50	1.20±0.05[a]	5.72±0.62[a]	11.74±0.45[a]	10.64±0.62[a]	12.94±0.28[a]
Gln 40+ BPA50	0.73±0.04*	6.97±0.55*	15.91±1.76*	13.81±0.53*	16.33±1.55*
Gln80+ BPA50	0.40±0.02**	9.77±0.19**	22.03±2.19**	18.73±1.21**	24.91±3.62**

MDA: Malondialdehyde, GSH: Glutathione, CAT: Catalase, SOD: Superoxide dismutase, GPx: Glutathione peroxidase, BPA: Bisphenol A, Gln: Glutamine

[a] ($p<0.001$) Significant difference when compared with the control group.

[b] ($p<0.05$) [c] ($p<0.01$) [d] ($p <0.001$) Significant difference when compared with the BPA group.

Effect of Gln on the kidney histology of rats treated with BPA

The kidneys of the control group and Gln (80 mg/kg) administered group had normal glomeruli and renal tubules (Figures 1A and B). However, the kidneys of BPA-administered rats showed collapsed glomerulus, widened Bowman's space, lipid accumulation, and tubular necrosis (Figure 1C). The kidneys of rats supplemented with Gln (20 and 40 mg/kg) showed widened Bowman's space and tubular necrosis (Figures 1D and 1E). The kidneys of rats supplemented with 80 mg/kg Gln showed normal glomerulus and renal tubule (Figure 1F).

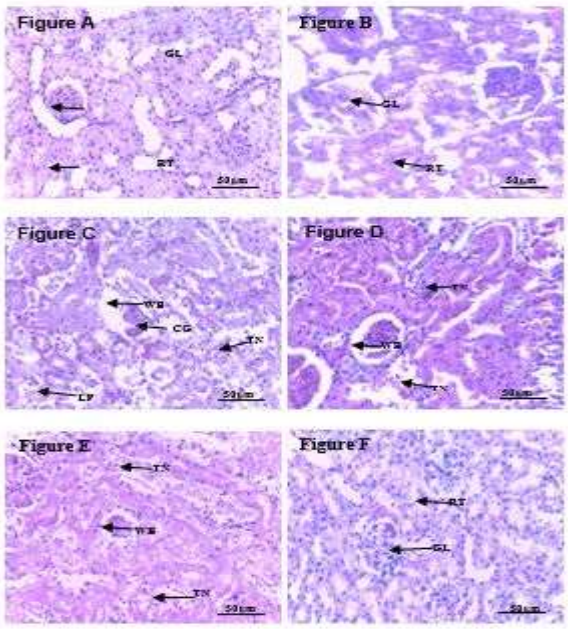

Figure1: Kidney micrographs obtained from rats in different study groups. A: Control, B: Treatment with PBA (50 mg/kg), C: Treatment with glutamine (20 mg/kg) + bisphenol A (50 mg/kg), D: Treatment with glutamine (40 mg/kg) + bisphenol A (50 mg/kg), E: Treatment with glutamine (80 mg/kg) +bisphenol A (50 mg/kg). GL: Normal glomerulus, RT: Normal renal tubule, TN: Tubular necrosis, LP: Lipid accumulation, WB: Widened Bowman's Space, CG: Collapsed glomerulus

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Discussion

This study explored the ability of Gln to prevent BPA-induced kidney damage in rats. In the present study, BPA decreased body weight and increased kidney weight. This observation confirmed earlier reports, which showed a decrease in the body weight and an increase in the kidney weight of BPA (40mg/kg)-administered rats (18). In this study, BPA incapacitated kidney function by stimulating high serum levels of urea, creatinine, and uric acid with low levels of serum electrolytes. This observation is in agreement with the dysfunctional levels of the aforementioned parameters reported in BPA (50 mg/kg -150 mg/kg) - induced renal damage in rats (8). Moreover, BPA caused notable impairment in the functional abilities of kidney antioxidants characterized by depleted levels of SOD, GPx, CAT, and GSH. Similarly, Kobroob reported low levels of kidney antioxidants in BPA-administered rats (8). One of the attributes of drug-induced renal damage is the occurrence of lipid peroxidation. In our study, lipid peroxidation was conspicuous in the kidneys of BPA-treated rats, marked by elevated levels of MDA. In line with this finding, Edres et al. reported elevated kidney MDA levels in BPA-induced kidney dysfunction (18).

In the present study, we observed tubular necrosis, collapsed glomerulus, widened Bowman's space, and lipid accumulation in the kidneys of BPA-treated rats. This is in agreement with a previous study conducted by Korkmaz et al. (24). Several speculated mechanistic factors have been associated with BPA-induced renal dysfunction. In 2013, Manikkam et al. attributed this to the accumulation of BPA toxic metabolites and the inability of the kidneys to excrete the metabolites (25). The accumulated toxic metabolites can alter kidney morphology, thereby impairing kidney function. Bosch-Panadero et al. associated BPA-induced renal damage with mitochondrial injury, oxidative stress, and the apoptosis of kidney cells (26). Mourad and Khadrawy suggested that renal pathology caused by BPA might be due to the generation of reactive oxygen species by its metabolites (27). In the present study, Gln supplementation prevented BPA-induced renal damage in a dose-dependent manner. This was characterized by restored levels of serum renal biochemical markers and decreased kidney MDA levels. It was also accompanied by increased kidney antioxidants and restored kidney morphology. Similarly, in a study by Brovodan et al. (13), Gln restored renal function in acetaminophen-treated rats. Sadar et al. also reported that Gln protected against diabetes-induced nephropathy in rats (14). In contrast with these findings, some studies claimed that Gln did not prevent cisplatin- (28) and cyclophosphamide (29)-induced nephrotoxicity in rats. In this study, restored kidney function due to Gln supplementation might be attributed to its antioxidant activity. Since Gln is a substrate for the synthesis of GSH, which is the most abundant cellular thiol and antioxidant (30), the administration of Gln might have increased GSH synthesis, thus inhibiting oxidative stress (31). Moreover, GSH is an antioxidant that scavenges electrophilic and oxidant species directly or through enzymatic catalysis. It quenches reactive hydroxyl free radicals as well as other oxygen-centered free radicals. It is the co-substrate of GPx that inactivates peroxides (hydrogen and lipid peroxides) (32). Furthermore, Gln might have decreased renal production of pro-inflammatory mediators and renal cell apoptosis, which have been associated with BPA-induced renal dysfunction. Studies revealed that Gln produces anti-inflammatory effects by decreasing the expression of pro-inflammatory cytokines (33).

Conclusion

Based on the results, it can be concluded that Gln supplementation prevents BPA-induced alterations in renal serum biochemical markers, oxidative stress, and kidney histology in a dose-dependent manner. It may have beneficial application for the management of BPA-associated renal dysfunction.

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Ethical statement

The rats were handled according to the Guide for the Use of Laboratory Animals. Approval was obtained from the Research Ethics Committee of the Department of Pharmacology, Faculty of Pharmacy, Madonna University (approval code: REC/PHARM/013/2022).

Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Both authors contributed to the study design, data collection, analysis, and writing of the final manuscript.

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