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Ameliorative Role of Glutathione in Postinor-2 Induced Kidney Damage Using Sprague-Dawley Rats

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Abstract

Background: Levonorgestrel, an emergency oral drug, prevents unwanted pregnancies after unprotected sexual intercourse. It functions similarly to progesterone, allowing for the prevention of pregnancy if administered within a stipulated period. Glutathione is an antioxidant that protects against free radicals and xenobiotic substances.

Objectives: This study investigated the effects of levonorgestrel and glutathione (GSH) on kidneys through biochemical, histological, and functional analyses.

Methods: Forty Sprague-Dawley rats were divided into four groups (n = 10). Group A served as the control group and was administered 1 ml of distilled water. Group B was administered 1 ml of 1.5 mg/100 ml of levonorgestrel, group C was administered 2 ml of 1.5 mg/100 ml of levonorgestrel, and group D was administered 4 ml of 1.5 mg/100 ml of levonorgestrel. Five rats from each group were euthanized at the end of the first treatment period. The remaining five rats in each group were administered GSH (100 mg/kg).

Results: Levonorgestrel administration increased creatinine, decreased urea and albumin, decreased superoxide dismutase and catalase levels, and increased malondialdehyde levels in rats. Rats administered levonorgestrel alone showed nephrological vascular congestion and mild tubular necrosis. Glutathione administration reversed the effects of levonorgestrel on the kidneys.

Conclusion: Glutathione has some ameliorative effects on levonorgestrel-induced toxicity in the kidney due to its antioxidant function.

Keywords: Levonorgestrel; Glutathione; Kidney function; Histology; Oxidative stress

Introduction

Postinor® is a contraceptive pill containing 0.75 mg of progesterone levonorgestrel, a steroid lipid molecule with a 3-hydroxylated estrane structure [1]. It is a water-insoluble, hydrophobic, and relatively neutral molecule that works similarly to progesterone [2], preventing pregnancy if taken within an appropriate timeframe [3, 4]. Levonorgestrel, also known as the morning-after pill, is a first-line oral contraceptive pill approved by the World Health Organization to prevent pregnancy [5]. It is accessible over the counter without a prescription and has been approved by the FDA for use by people of all ages because of its absence of life-threatening adverse effects [6]. The most prevalent adverse effects of the drug include irregular cycles of menstruation, amenorrhea, dysmenorrhea, oligomenorrhea, migraines, and acne [7, 8]. Levonorgestrel does not protect patients against sexually transmitted illnesses [9].

Glutathione, a tripeptide composed of cysteine, glycine, and glutamate [10], is essential for various physiological activities and is a key immune system builder, antioxidant, and detoxifier [11, 12]. It is an antioxidant that prevents age-related pro-oxidizing changes in the redox state and converts free radical H2O2 into harmless molecules [13]. Glutathione also regulates detoxification processes [14] and the cell cycle [15], and its depletion can lead to DNA lesions, chromosomal damage, genetic mutations, and cellular apoptosis [16]. Changes in glutathione concentration are a common sign of various clinical illnesses [17, 18].

The kidney plays a crucial role in maintaining the body's water volume, electrolyte balance, and acid-base balance [19]. It also excretes metabolic products and harmful substances [20, 21]. Renal function tests assess renal function, including blood flow, glomerular filtration, and tubular function [22, 23]. The kidney is vulnerable to oxidative stress due to its abundance of mitochondria [24, 25]. Drug-induced tubular necrosis caused by medications increases the generation of reactive oxygen species in the renal tubules. However, when these medications interact with glutathione, ROS production decreases [26].

Kidneys play a crucial role in the excretion of several drug classes, and their use puts this system at risk [27]. Kidney function in filtration and clearance makes the renal system particularly vulnerable to adverse drug effects [28]. Hence, the aim of this study was to ascertain how glutathione may remedy renal impairment or injury resulting from the use of postinor-2.

Materials and Method

Care and Management of Animals

This study involved 40 adult female Sprague-Dawley rats weighing between 100 and 170 g. The rats were acclimatized for two weeks and maintained under standard conditions at Bowen University's Department of Anatomy Animal House. They were placed in well-ventilated plastic cages, fed pellets and water, and kept under hygienic conditions. Wood shavings were used daily as bedding for proper sanitation.

Drug Dilution

The drug, containing 0.75 mg of levonorgestrel, was dissolved in 0.1 liters of distilled water and stored until needed.

Experimental design

Forty adult Sprague-Dawley rats were used as experimental models and divided into groups A-D. Each group consisted of ten randomly selected rats.

Group A served as the control, and the animals were administered 1 mL of distilled water.

Group B served as a low dose, and the animals were administered 1 mL of 1.5 mg/100 mL of postinor-2.

Group C served as a medium dose, and the animals were given 2 mL of 1.5 mg/100 mL of postinor-2.

Group D served as a high dose, and the animals were administered 4 mL of 1.5 mg/100 mL of postinor-2.

After four weeks of administration of postinor-2, five rats were randomly selected from each group and euthanized using ketamine, and their kidneys were harvested for histology and oxidative stress markers. Blood was collected from the ocular sinuses for analysis. The remaining five rats were administered 100 mg/kg glutathione as an antioxidant for 2 weeks before euthanization.

Blood sampling and function test: Blood was collected from the ocular sinus using capillary tubes and centrifuged, and the kidneys for oxidative stress were frozen at -80°C before homogenization.

Histological Procedures: The kidneys were collected, fixed, and processed for histology using a standard protocol. Four micrometer-thick paraffin sections were created for microscopic examination.

Statistical Analysis: GraphPad Prism software was used to compute, analyze, and summarize data, with results expressed as mean ± SEM. One-way ANOVA and Newman-Keuls post hoc statistical tests were used, with $P<0.05$.

Results

Effects of Administration of Levonorgestrel and Glutathione on Body Weight

A significant increase in body weight was observed in all groups. Table 1 shows the average weight of the rats in each group and the percentage increase in weight.

Effects of Administration of Levonorgestrel and Glutathione on Kidney Weight Analysis

The study found that rats treated with levonorgestrel had a significantly lower average kidney weight compared to the control group, while those treated with glutathione had weightier-average kidneys compared to those treated with similar doses of levonorgestrel, as shown in Table 2.

Effects of Administration of Levonorgestrel and Glutathione on Renal Function

Table 3 shows that levonorgestrel treatment led to a dose-dependent increase in creatinine concentration and a decrease in urea and albumin levels compared to the control group. After levonorgestrel treatment, glutathione administration resulted in a dose-dependent decrease in urea and an increase in albumin, but creatinine levels showed no significant decrease when compared to their counterparts treated with similar doses of levonorgestrel.

Effects of Administration of Levonorgestrel and Glutathione on Renal Biochemical Stress Markers

The study found that Levonorgestrel treatment significantly increased malondialdehyde (MDA) concentrations and decreased catalase and superoxide dismutase concentrations after four weeks. However, MDA levels were lower in groups treated with glutathione for an additional two weeks, and those treated with glutathione showed higher levels of SOD and CAT than those treated with levonorgestrel alone (Table 4).

Table 1: Effects of administration of levonorgestrel and glutathione on the body weight of the animals

GROUPS	BEFORE ADMINISTRATION (g)	AFTER ADMINISTRATION (g)	% WEIGHT DIFFERENCE
Control	91.97 ± 24.64	159.50 ± 14.18	73.43%
Low Dose Levonorgestrel	97.33 ± 13.47	140.33 ± 5.54	44.18%
Medium Dose Levonorgestrel	110.00 ± 30.12	157.33 ± 36.13	43.03%
High Dose Levonorgestrel	111.83 ± 12.88	150.83 ± 7.70	34.87%
Control	84.50 ± 8.46	153.95 ± 16.34	82.19%
Low Dose Levonorgestrel + Glutathione	95.83 ± 10.93	163.28 ± 11.59	70.39%
Medium Dose Levonorgestrel + Glutathione	102.83 ± 25.02	165.72 ± 33.40	61.16%
High Dose Levonorgestrel + Glutathione	126.17 ± 29.36	172.52 ± 28.74	36.59%

Values are mean ± standard error of mean; n=5

Table 2: Effects of administration of levonorgestrel and glutathione on the average kidney weight

Group	Average Kidney Weight (g)
Control	1.17 ± 0.14
Low Dose Levonorgestrel	0.93 ± 0.18
Medium Dose Levonorgestrel	0.97 ± 0.20
High Dose Levonorgestrel	0.98 ± 0.11
Control	0.88 ± 0.19
Low Dose Levonorgestrel + Glutathione	1.18 ± 0.14
Medium Dose Levonorgestrel + Glutathione	1.03 ± 0.14
High Dose Levonorgestrel + Glutathione	1.12 ± 0.21

Values are mean ± standard error of mean

Table 3: Effects of administration of levonorgestrel and glutathione on some kidney function parameters

Group	CREATININE (mg/dL)	UREA (mg/dL)	ALBUMIN (mg/dL)
Control	13.60 ± 0.12	47.73 ± 0.13	23.94 ± 0.03
Low Dose Levonorgestrel	15.20 ± 0.67	40.62 ± 0.36	23.35 ± 0.05
Medium Dose Levonorgestrel	15.70 ± 0.14	35.36 ± 3.00	20.89 ± 0.23
High Dose Levonorgestrel	18.90 ± 0.17	26.29 ± 1.12	17.29 ± 0.76
Control	13.69 ± 1.02	48.16 ± 0.16	24.07 ± 1.00
Low Dose Levonorgestrel + Glutathione	14.53 ± 0.12	44.24 ± 0.30	28.30 ± 0.01
Medium Dose Levonorgestrel + Glutathione	14.42 ± 0.26	39.27 ± 1.07	32.26 ± 0.06

High Dose Levonorgestrel + Glutathione	14.19 ± 0.94	35.12 ± 0.03	49.97 ± 0.05

Values are mean ± standard error of mean

Table 4: Effects of administration of levonorgestrel and glutathione on renal biochemical stress markers

Group	MDA (nmol/mg)	SOD (min/mg)	CAT (nmol/mg)
Control	405.5 ± 2.06	120.04 ± 0.16	268.72 ± 0.32
Low Dose Levonorgestrel	423.99 ± 0.19	109.03 ± 1.48	216.54 ± 0.99
Medium Dose Levonorgestrel	449.99 ± 0.02	90.89 ± 0.29	206.84 ± 1.07
High Dose Levonorgestrel	468.07 ± 1.07	85.65 ± 0.01	165.01 ± 0.45
Control	401.36 ± 1.71	122.51 ± 0.31	283.41 ± 0.29
Low Dose Levonorgestrel + Glutathione	406.40 ± 1.72	179.05 ± 0.65	242.57 ± 1.08
Medium Dose Levonorgestrel + Glutathione	439.13 ± 3.02	196.50 ± 1.44	238.11 ± 0.46
High Dose Levonorgestrel + Glutathione	453.21 ± 1.05	219.54 ± 1.69	218.55 ± 1.19

Values are mean ± standard error of mean

Effects of Administration of Levonorgestrel and Glutathione on the Histology of the Kidney

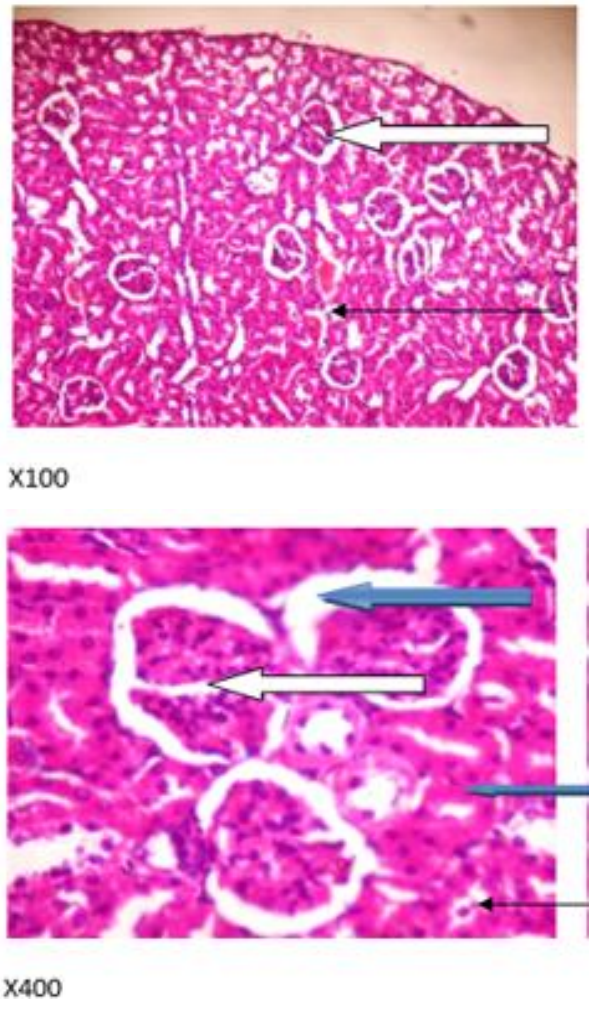
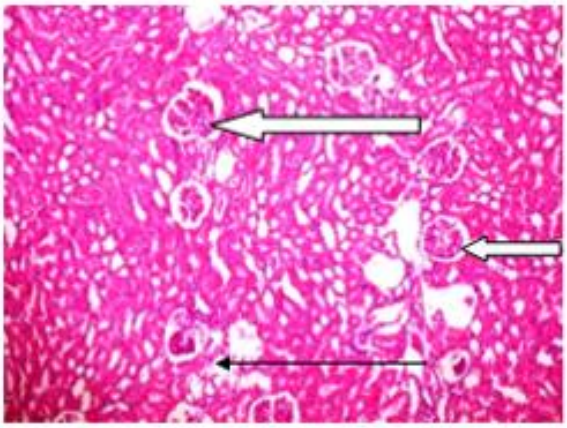


Plate 1: Photomicrographs of kidney sections from the control group show normal architecture with normal glomeruli, mesangial cells, capsular spaces (white arrow), renal tubules (blue arrow), and interstitial spaces (slender arrow) in the renal cortex.



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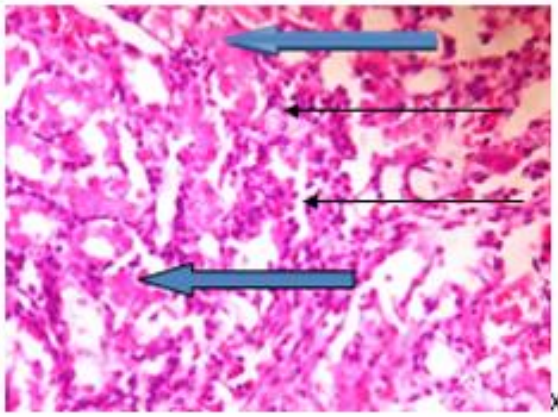

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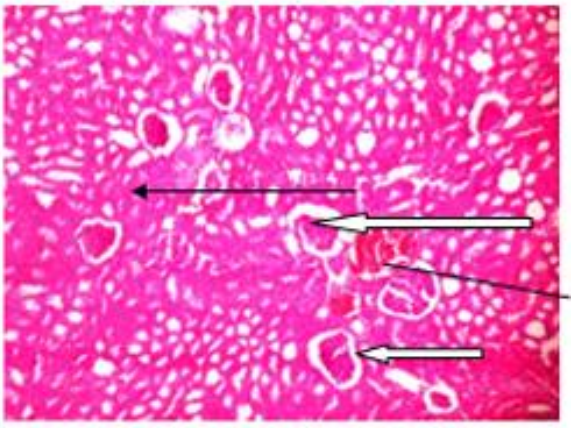
Plate 2: Photomicrographs of kidney sections from the low-dose levonorgestrel group show poor architecture, with normal glomeruli, mesangial cells, capsular spaces (white arrow), eosinophilic cells filled renal tubules (blue arrow), and moderately infiltrated interstitial spaces (slender arrow) in the renal cortex.



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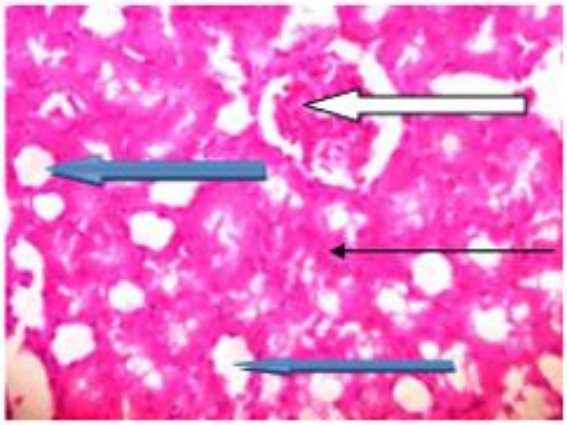

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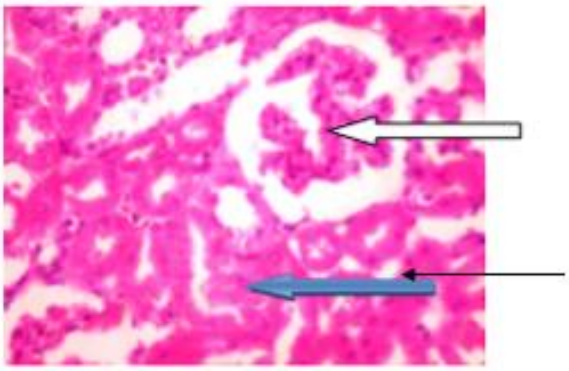
Plate 3: Photomicrographs of kidney sections from the medium-dose levonorgestrel group revealed moderately normal architecture with normal glomeruli, mesangial cells, and capsular spaces (white arrow), normal renal tubules (blue arrow), and mild vascular congestion in the interstitial spaces (slender arrow).



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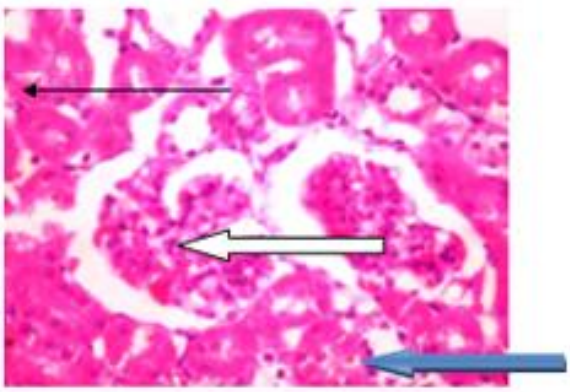

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Plate 4: Photomicrographs of kidney sections from the high-dose levonorgestrel group show moderately normal architecture, with normal glomeruli with mesangial cells and capsular spaces (white arrow), mild tubular necrosis (blue arrow), and vascular congestion (slender arrow) in the renal cortex.

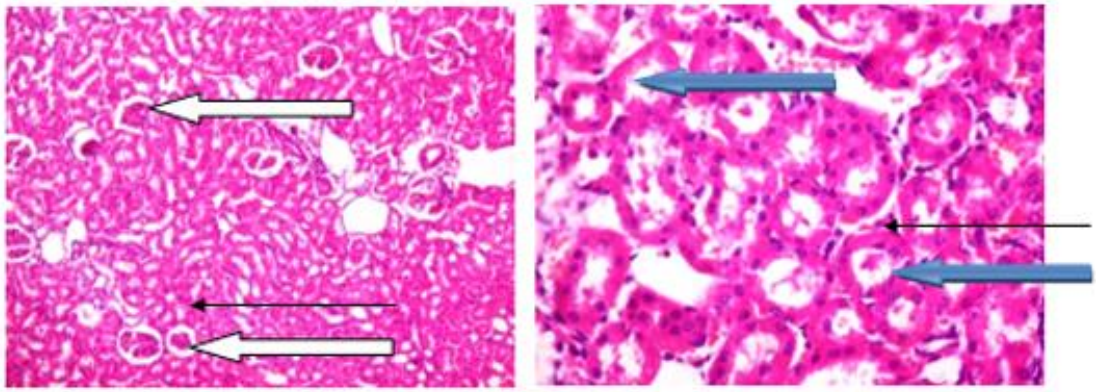

Plate 5: Photomicrographs of kidney sections from the control group administered distilled water for 6 weeks. The renal cortex shows normal glomeruli with normal mesangial cells and capsular spaces (white arrow), renal tubules (blue arrow), and interstitial spaces (slender arrow).

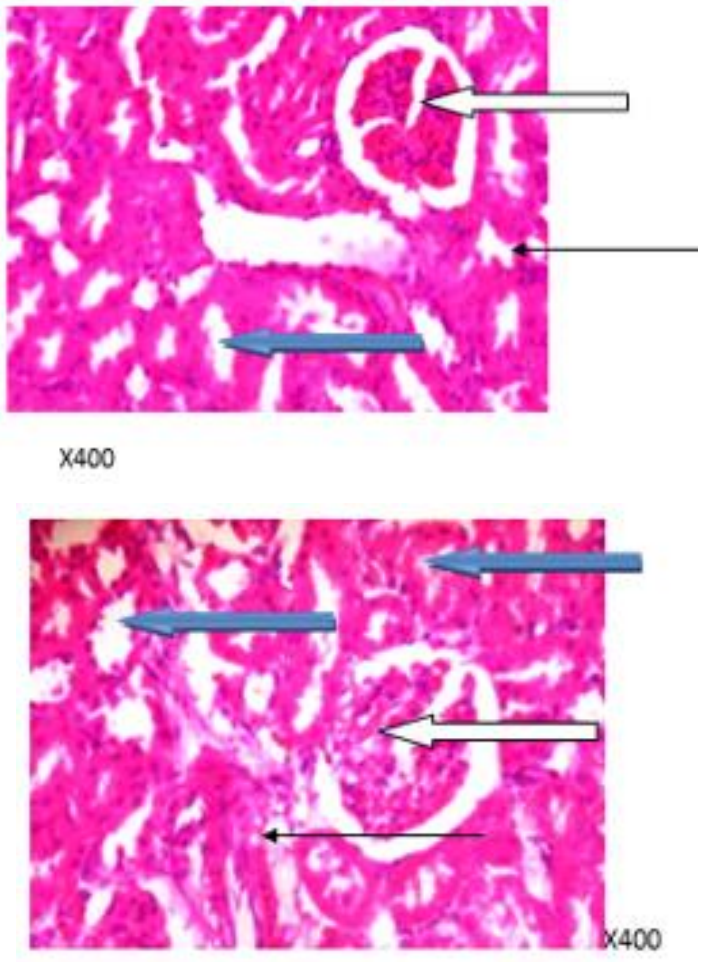

Plate 6: Photomicrographs of kidney sections from low-dose levonorgestrel treated with glutathione revealed normal glomeruli with mesangial cells and capsular spaces (white arrow), normal renal tubules (blue arrow), and interstitial spaces (slender arrow).

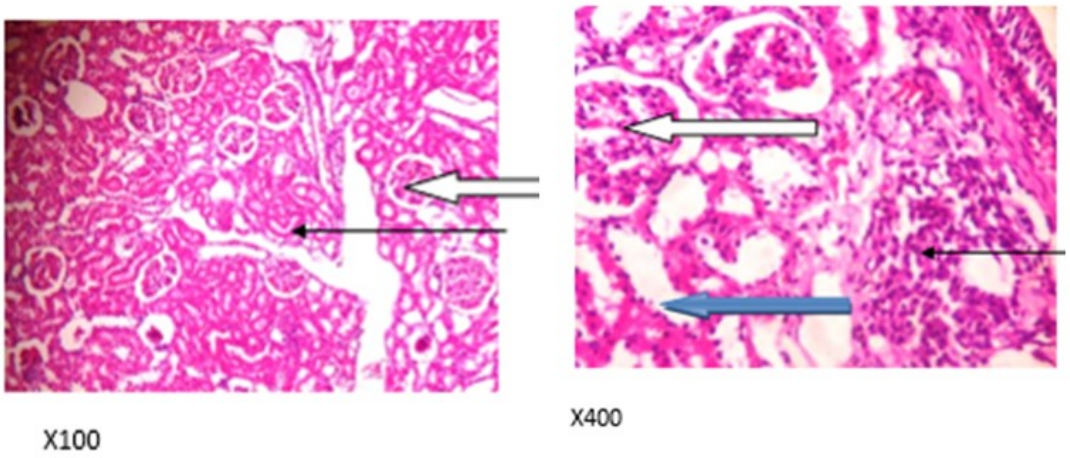

Plate 7: Photomicrographs of kidney sections from medium-dose levonorgestrel treated with glutathione reveal normal glomeruli with mesangial cells and capsular spaces (white arrow), normal renal tubules (blue arrow), and interstitial spaces with an area of inflammatory cells (slender arrow).

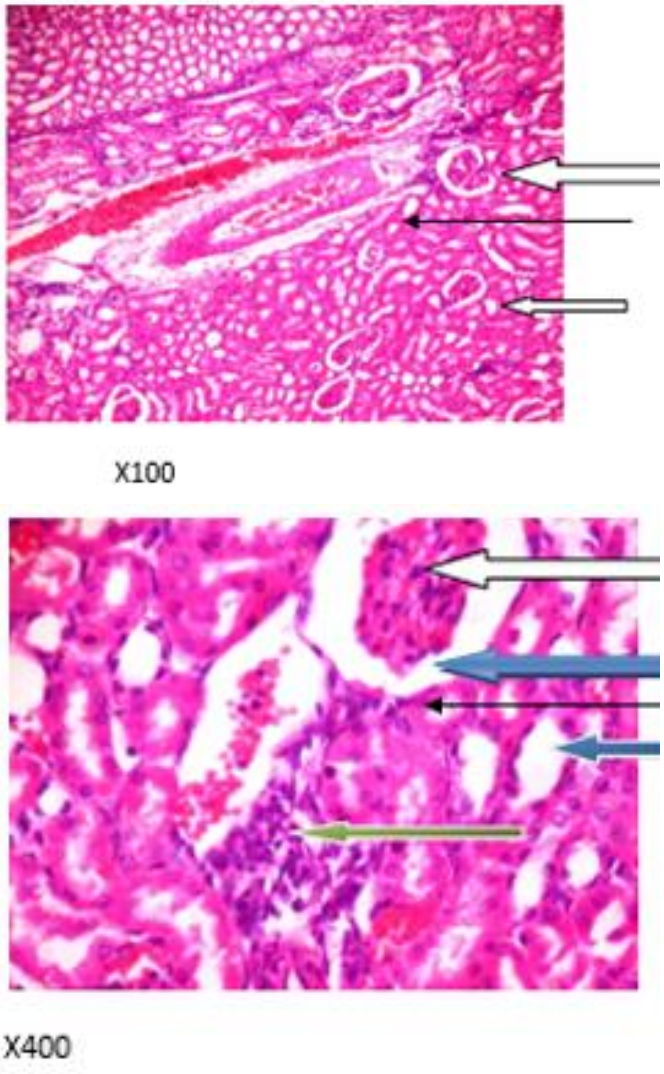

Plate 8: Photomicrographs of kidney sections from high-dose levonorgestrel treated with glutathione revealed normal glomeruli (white arrow), normal renal tubules (blue arrow), and mild perivascular infiltration of inflammatory cells in the renal cortex and interstitial spaces (green arrow).

Discussion

Oral contraceptives prevent pregnancy but can cause kidney impairment and injury owing to their consistent use or abuse [29, 30]. Glutathione plays a crucial role in biotransformation, protecting individuals from reducing agents [31] and aiding in immune system function, tissue repair [32], detoxification, binding electrophiles [33], and regulating metabolic pathways essential for homeostasis 10. Consistent abuse can lead to increased concentrations of the chemicals excreted [34].

Creatinine, a vital excretory product of muscular activity, is closely associated with renal function [35]. In rats treated with levonorgestrel, creatinine levels increased, whereas rats subsequently administered glutathione showed a decrease. Increased serum creatinine concentrations may be indicative of a decrease in glomerular filtration rate [23], which may signal severe renal damage or disease [22]. Glutathione may be effective in restoring kidney filtration, hence reducing serum creatinine.

Urea is a major nitrogen-containing metabolic product [36]. Its serum concentration decreased in rats treated with levonorgestrel and further decreased in rats administered glutathione afterward. This may indicate abnormal urea excretion [37].

Albumin, a carrier protein [38], showed a decrease in serum concentration in rats treated with levonorgestrel, while an increase was observed in rats treated with glutathione afterward. Soeters et al. (2019) suggested that an increase or decrease in serum albumin concentration points to an electrolyte imbalance, potentially indicating compromised renal balance [39].

This study found that rats treated with levonorgestrel had significantly increased malondialdehyde levels in their kidneys, which is a diagnostic tool for oxidative damage. Alcohol abuse has also been associated with an increase in malondialdehyde concentration [40], which is accompanied by advancements in renal disease [41]. Our study revealed that rats treated with glutathione after levonorgestrel administration showed a significant decline in malondialdehyde levels compared to rats treated with only postinor-2. This is consistent with Tualeka et al. (2019), who stated that glutathione and malondialdehyde levels have a substantial reciprocal correlation [42].

The decreased superoxide dismutase levels in rats treated with levonorgestrel might indicate lipid peroxidation and oxidative stress [43]. Glutathione administration reversed this decrease and increased SOD levels beyond that of the control group. As proposed by Huo et al. (2021), the increase in SOD may be the result of physical protection against excess ROS [44]. This suggests that glutathione has ameliorative effects on levonorgestrel-induced renal damage.

Catalase, an essential enzyme that protects cells from oxidative damage, also decreased following levonorgestrel treatment. Similarly, alcohol abuse is associated with a decrease in catalase levels [40]. According to Hong and Park (2021), a decrease in catalase levels renders the kidney vulnerable to oxidative tissue damage and renal fibrosis [45]. Our study suggests that glutathione may restore catalase levels previously depleted by levonorgestrel treatment.

Renal vascular congestion and mild renal tubular necrosis were observed with an increase in the levonorgestrel dosage. According to Deferrari et al. (2021), this can be attributed to drug reactions [46]. Renal congestion raises renal interstitial pressure, affecting the capillary bed and tubules and potentially causing local hypoxia [47]. Renal congestion worsens acute kidney injury by reducing blood flow velocity in the peritubular capillaries [48]. Experimental rats treated with glutathione showed normal cytoarchitecture and inflammatory cells in the interstitial spaces of the kidneys. The kidney has intrinsic repair capacity through a process involving various cell types, including surviving proximal tubular cells, inflammatory cells, and fibroblasts [49]. The reconstitution of normal renal cytoarchitecture and tubules may indicate an ameliorative effect of glutathione on levonorgestrel-induced hepatic histological damage.

Conclusion

Consistent use of levonorgestrel damages kidney cytology and function, but glutathione treatment reverses kidney cytoarchitecture towards normalcy and reduces oxidative stress. Owing to the antioxidant properties of glutathione, the adverse effects of postinor-2 on the kidney can be ameliorated.

Source of Funding

The funding for this study was contributed by all the authors involved

Conflicts of Interest

The authors declare that they have no competing interests.

Ethical Approval

This study was approved by Bowen University Institutional Research Ethics Committee on the 8th of June, 2023 with BUI/COHES/ANA/01024. The care of the experimental animals was by the guidelines of the Institution's Ethics Committee.

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Author Contributions

OAA conceived and designed the study, and provided funding. JHO analysed and interpreted data, and provided funding. PKA provided research materials and logistic support. NEB wrote initial and final draft of article, and provided funding. RIO conducted research, collected and organized data, and provided funding. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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