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Ameliorative Potency of Glutathione in Levonorgestrel-Induced Kidney Damage Using Sprague-Dawley Rats

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ABSTRACT:

Levonorgestrel is an emergency contraceptive that prevents unwanted pregnancies after unprotected sexual intercourse. It works similarly to progesterone and can prevent pregnancy if taken within a specific period. Glutathione, on the other hand, is an antioxidant that protects against free radicals and harmful substances. This study examined the effects of levonorgestrel and glutathione (GSH) on the kidneys through biochemical, histological, and functional analyses. The study involved forty Sprague-Dawley rats divided into eight groups. Three groups were administered graded doses of levonorgestrel for 4 weeks, while 3 others were administered levonorgestrel for 4 weeks followed by glutathione for 2 weeks. Two control groups were also included, one receiving distilled water for 4 weeks and the other for 6 weeks. The results showed that levonorgestrel affected the rats' kidneys by increasing creatinine, reducing urea and albumin, lowering superoxide dismutase and catalase levels, and increasing malondialdehyde levels. Rats administered only levonorgestrel displayed kidney vascular congestion and mild tubular necrosis. However, the administration of glutathione reversed the effects of levonorgestrel on the kidneys, showing that glutathione has some ameliorative effects on levonorgestrel-induced kidney toxicity due to its antioxidant function.

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

1. Introduction

Postinor® is a contraceptive pill containing 0.75 mg of progesterone levonorgestrel, a steroid lipid molecule with a 3-hydroxylated estrane structure (Adigun et al., 2016). It is a water-insoluble, hydrophobic, and relatively neutral molecule that works similarly to progesterone (Farahmandghavi et al., 2019), preventing pregnancy if taken within an appropriate timeframe (Peck et al., 2016; Keegan, 2019). Levonorgestrel, also known as the morning-after pill, is a first-line oral contraceptive pill approved by the World Health Organization to prevent pregnancy (Endler et al., 2022). It is accessible over the counter without a prescription and has been approved by the FDA for people of all ages because of its absence of life-threatening adverse effects (Adashi et al., 2023). The most prevalent adverse effects of the drug include irregular cycles of menstruation, amenorrhea, dysmenorrhea, oligomenorrhea, migraines, and acne (Regidor, 2018; VanAtta et al., 2023). Levonorgestrel does not protect patients against sexually transmitted illnesses (Shen et al., 2019).

Glutathione, a tripeptide composed of cysteine, glycine, and glutamate (Polonikov, 2020), is essential for various physiological activities and is a key immune system builder, antioxidant, and detoxifier (Pompella and Corti, 2015; Pruteanu et al., 2023). It is an antioxidant that prevents age-related pro-oxidizing changes in the redox state and converts free radical H_2O_2 into harmless molecules (Mandal et al., 2022). Glutathione also regulates detoxification processes (Biswas et al., 2020) and the cell cycle (Hendrix et al., 2020), and its depletion can lead to DNA lesions, chromosomal damage, genetic mutations, and cellular apoptosis (Kankaya et al., 2023). Changes in glutathione concentration are a common sign of various clinical illnesses (Vairetti et al., 2021; Hristov, 2022).

The kidney plays a crucial role in maintaining the body's water volume, electrolyte balance, and acid-base balance (Nagami and Hamm, 2017). It also excretes metabolic products and harmful substances (Bajaj et al., 2018; Cameron, 2022). Renal function tests assess renal function, including blood flow, glomerular filtration, and tubular function (Mullens et al., 2020; Kellum et al., 2021). The kidney is vulnerable to oxidative stress due to its abundance of mitochondria (Aranda-Rivera et al., 2021; Tirichen et al., 2021). 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 (Gyurászová et al., 2020).

Kidneys play a crucial role in the excretion of several drug classes, and their use puts this system at risk (Alhassani et al., 2021). Kidney function in filtration and clearance makes the renal system particularly vulnerable to adverse drug effects (Deskur-Śmielecka et al., 2019). Hence, this study aimed to ascertain how glutathione may remedy renal impairment or injury resulting from the use of postinor-2.

2. Materials and Methods

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

45 mg of levonorgestrel was dissolved in 3 liters of distilled water and stored until needed. And 3 g of glutathione was dissolved in 3 liters of distilled water.

Experimental design

Forty adult Sprague-Dawley rats were used as experimental models and divided into 8 groups. Each group consisted of 5 randomly selected rats.

Group A served as Control Group 1 and was administered 1 mL of distilled water for 4 weeks.

Group B rats were administered a low dose (1 mL of 1.5 mg/100 mL) of levonorgestrel for 4 weeks.

Group C rats were administered a medium dose (2 mL of 1.5 mg/100 mL) of levonorgestrel for 4 weeks.

Group D rats were administered a high dose (4 mL of 1.5 mg/100 mL) of levonorgestrel for 4 weeks.

Group E served as Control Group 2 and was administered 1 mL of distilled water for 6 weeks.

Group F rats were administered a low dose (1 mL of 1.5 mg/100 mL) of levonorgestrel for 4 weeks, then administered 100 mg/kg of glutathione for 2 weeks.

Group G rats were administered a medium dose (2 mL of 1.5 mg/100 mL) of levonorgestrel for 4 weeks, then administered 100 mg/kg of glutathione for 2 weeks.

Group H rats were administered a high dose (4 mL of 1.5 mg/100 mL) of levonorgestrel for 4 weeks, then administered 100 mg/kg of glutathione for 2 weeks.

After 4 weeks of treatment, the rats from group A-D were euthanized using ketamine. The rats from group E-H were euthanized using ketamine after 6 weeks of treatment administration. The kidneys were harvested for histology and oxidative stress markers. Blood was collected from the ocular sinuses for analysis.

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. 4 mm 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 $P<0.05$.

3. 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

GROUP	BEFORE ADMINISTRATION (g)	AFTER ADMINISTRATION (g)	% WEIGHT DIFFERENCE
Group A	91.97 ± 24.64	159.50 ± 14.18	73.43%
Group B	97.33 ± 13.47	140.33 ± 5.54	44.18%
Group C	110.00 ± 30.12	157.33 ± 36.13	43.03%
Group D	111.83 ± 12.88	150.83 ± 7.70	34.87%
Group E	84.50 ± 8.46	153.95 ± 16.34	82.19%
Group F	95.83 ± 10.93	163.28 ± 11.59	70.39%
Group G	102.83 ± 25.02	165.72 ± 33.40	61.16%
Group H	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)
Group A	1.17 ± 0.14
Group B	0.93 ± 0.18
Group C	0.97 ± 0.20
Group D	0.98 ± 0.11
Group E	0.88 ± 0.19
Group F	1.18 ± 0.14
Group G	1.03 ± 0.14
Group H	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)
Group A	13.60 ± 0.12	47.73 ± 0.13	23.94 ± 0.03
Group B	15.20 ± 0.67	40.62 ± 0.36	23.35 ± 0.05
Group C	15.70 ± 0.14	35.36 ± 3.00	20.89 ± 0.23
Group D	18.90 ± 0.17	26.29 ± 1.12	17.29 ± 0.76
Group E	13.69 ± 1.02	48.16 ± 0.16	24.07 ± 1.00
Group F	14.53 ± 0.12	44.24 ± 0.30	28.30 ± 0.01
Group G	14.42 ± 0.26	39.27 ± 1.07	32.26 ± 0.06
Group H	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)
Group A	405.5 ± 2.06	120.04 ± 0.16	268.72 ± 0.32
Group B	423.99 ± 0.19	109.03 ± 1.48	216.54 ± 0.99
Group C	449.99 ± 0.02	90.89 ± 0.29	206.84 ± 1.07
Group D	468.07 ± 1.07	85.65 ± 0.01	165.01 ± 0.45
Group E	401.36 ± 1.71	122.51 ± 0.31	283.41 ± 0.29
Group F	406.40 ± 1.72	179.05 ± 0.65	242.57 ± 1.08
Group G	439.13 ± 3.02	196.50 ± 1.44	238.11 ± 0.46
Group H	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

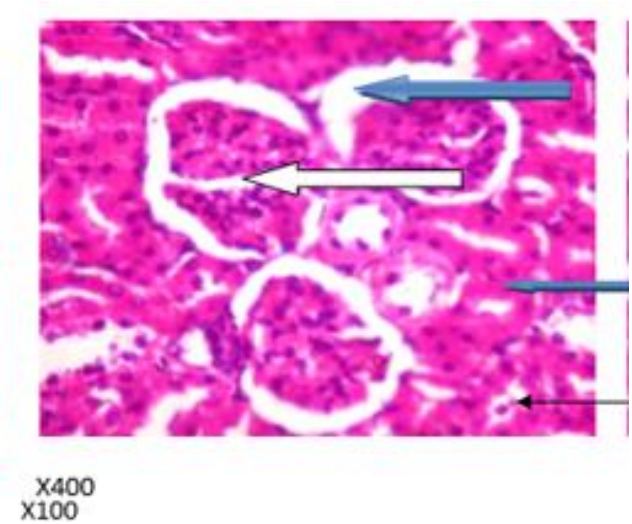

Figure 1: *Photomicrographs of kidney sections from the control group 1 show normal architecture with normal glomeruli, mesangial cells, capsular spaces (white arrow), renal tubules (blue arrow), and interstitial spaces (slender arrow) in the renal cortex.*

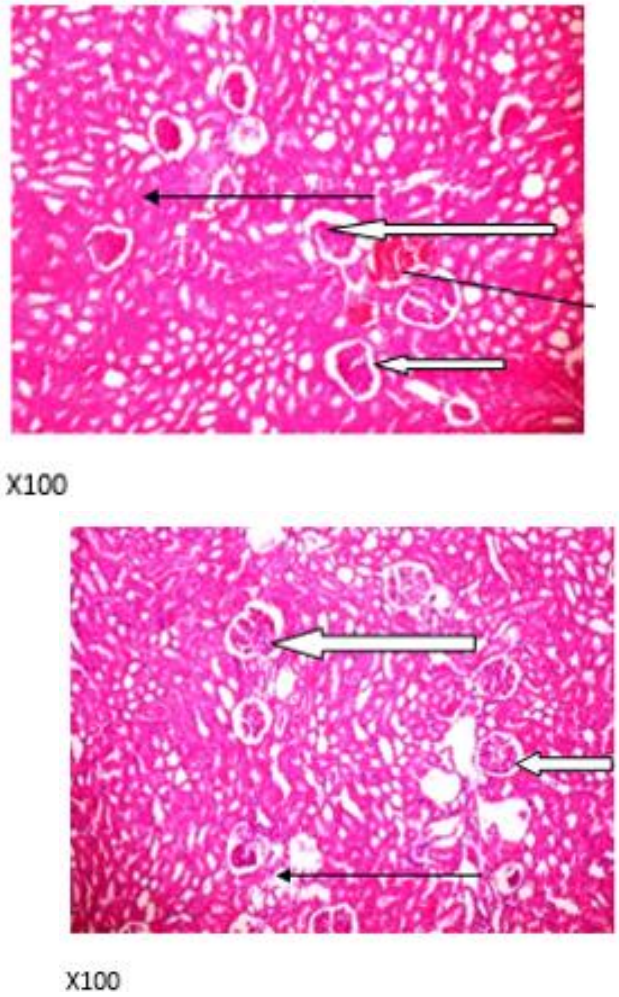

Figure 2*: Photomicrographs of kidney sections from the low-dose levonorgestrel group show poor architecture, with normal glomeruli, mesangial cells, capsular spaces (white arrow), eosinophilic cells filled renal tubules (blue arrow), and moderately infiltrated interstitial spaces (slender arrow) in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

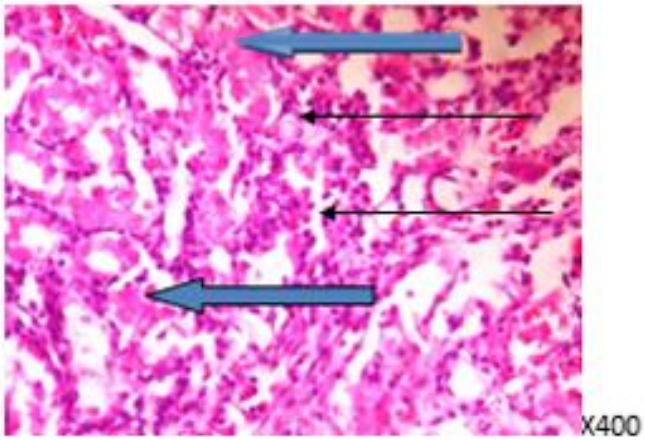

***Figure 3**: Photomicrographs of kidney sections from the medium-dose levonorgestrel group revealed moderately normal architecture with normal glomeruli, mesangial cells, and capsular spaces (white arrow), normal renal tubules (blue arrow), and mild vascular congestion in the interstitial spaces (slender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

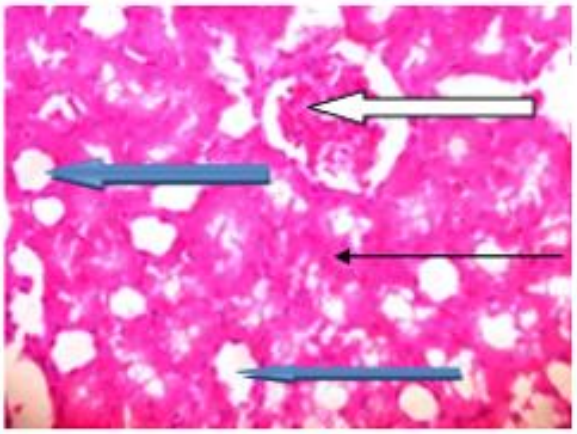

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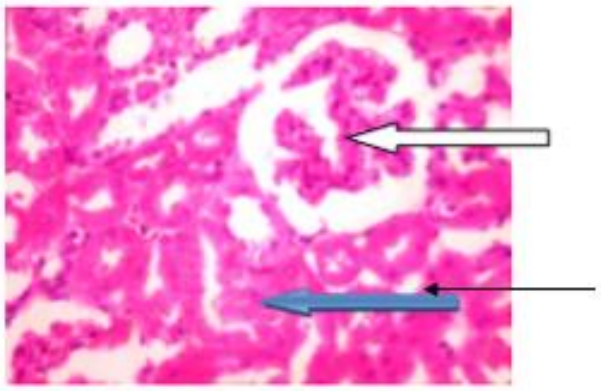
***Figure 4**: Photomicrographs of kidney sections from the high-dose levonorgestrel group show*



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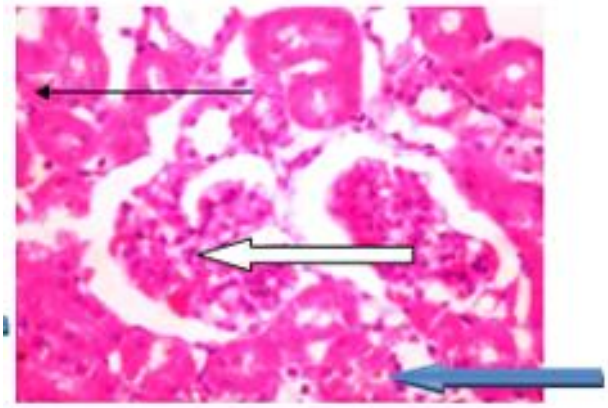

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moderately normal architecture, with normal glomeruli with mesangial cells and capsular spaces (white arrow), mild tubular necrosis (blue arrow), and vascular congestion (slender arrow) in the renal cortex.

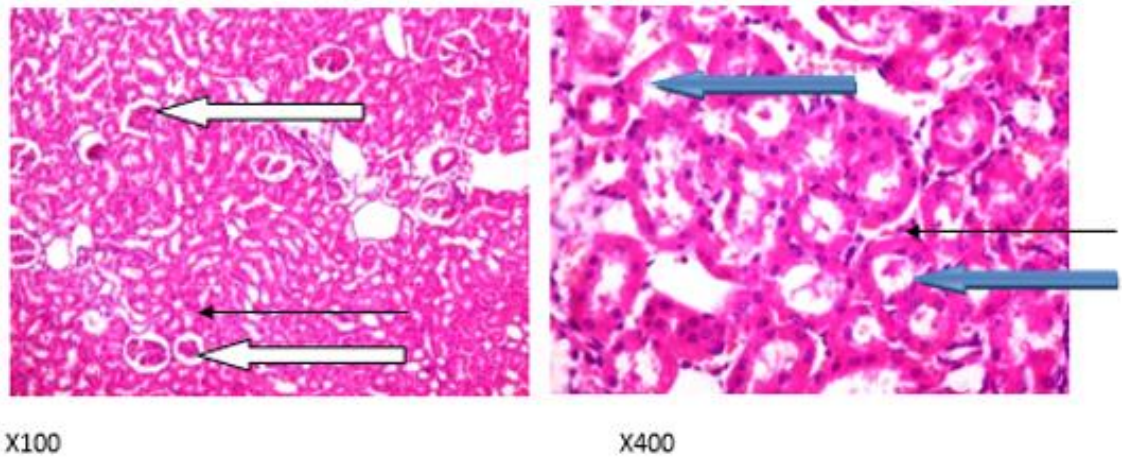

Figure 5*: Photomicrographs of kidney sections from the control group 2 administered distilled water for 6 weeks. The renal cortex shows normal glomeruli with normal mesangial cells and capsular spaces (white arrow), renal tubules (blue arrow), and interstitial spaces (slender arrow).*

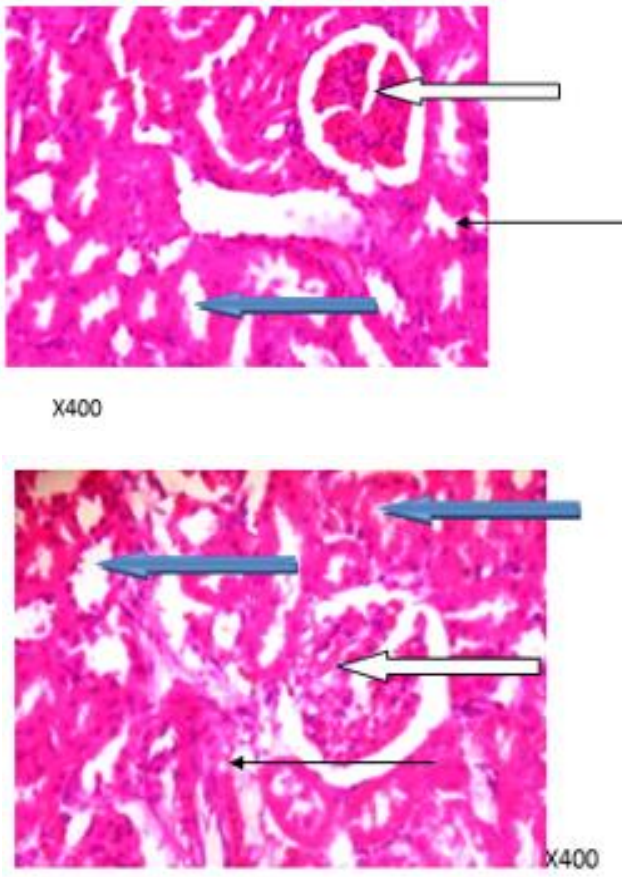

Figure 6*: Photomicrographs of kidney sections from low-dose levonorgestrel treated with glutathione revealed normal glomeruli with mesangial cells and capsular spaces (white arrow), normal renal tubules (blue arrow), and interstitial spaces (slender arrow).*

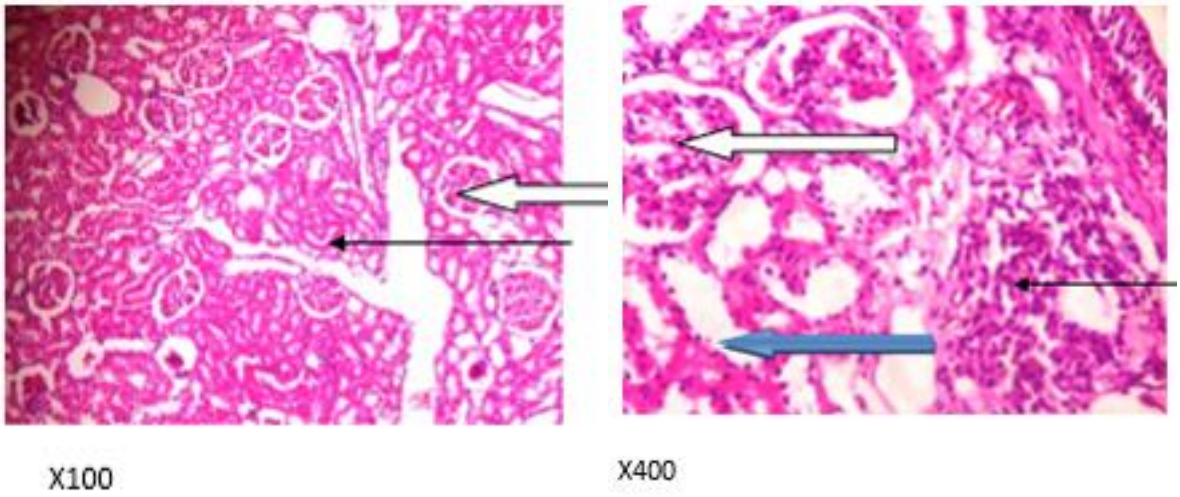

Figure 7: *Photomicrographs of kidney sections from medium-dose levonorgestrel treated with glutathione reveal normal glomeruli with mesangial cells and capsular spaces (white arrow), normal renal tubules (blue arrow), and interstitial spaces with an area of inflammatory cells (slender arrow).*

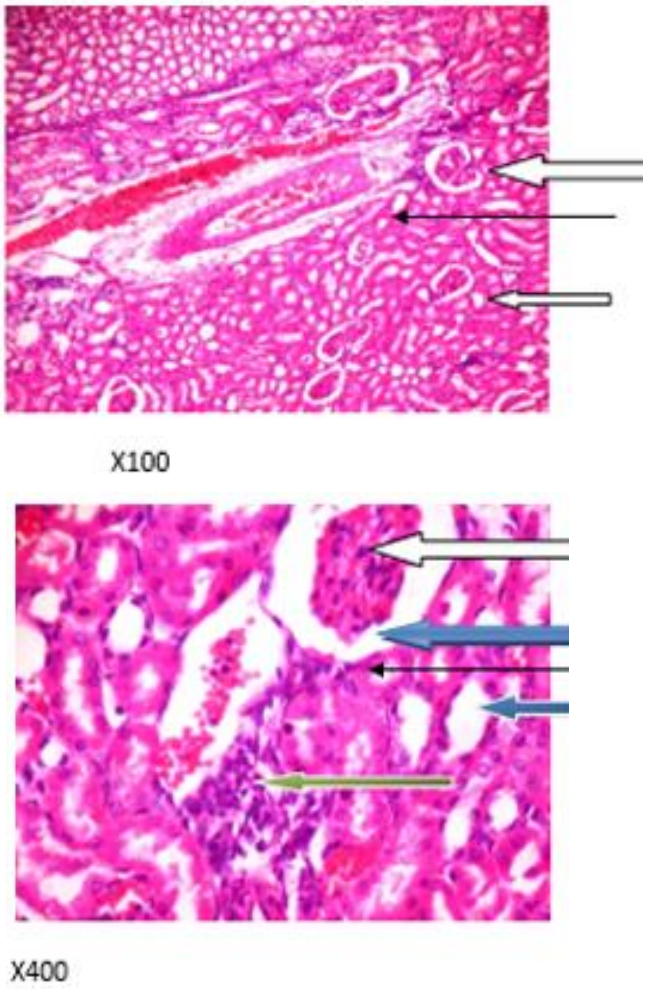

Figure 8*: Photomicrographs of kidney sections from high-dose levonorgestrel treated with glutathione revealed normal glomeruli (white arrow), normal renal tubules (blue arrow), and*

mild perivascular infiltration of inflammatory cells in the renal cortex and interstitial spaces (green arrow).

4. Discussion

Oral contraceptives prevent pregnancy but can cause kidney impairment and injury owing to their consistent use or abuse (Akinwumi et al., 2022; Ransome et al., 2022). Glutathione plays a crucial role in biotransformation, protecting individuals from reducing agents (Silvagno et al., 2020) and aiding in immune system function, tissue repair (Chiara, 2022), detoxification, binding electrophiles (Gad, 2014), and regulating metabolic pathways essential for homeostasis (Polonikov, 2020). Consistent abuse can lead to increased concentrations of the chemicals excreted (Barakat et al., 2021).

Creatinine, a vital excretory product of muscular activity, is closely associated with renal function (Rivadeneyra-Domínguez et al., 2018). 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 (Kellum et al., 2021), which may signal severe renal damage or disease (Mullens et al., 2020). Glutathione may be effective in restoring kidney filtration, hence reducing serum creatinine.

Urea is a major nitrogen-containing metabolic product (Allison, 2020). Its serum concentration decreased in rats treated with levonorgestrel and further reduced in rats administered glutathione afterward. This may indicate abnormal urea excretion (Yeun et al., 2019).

Albumin, a carrier protein (Spada et al., 2021), 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 an increase or decrease in serum albumin concentration points to an electrolyte imbalance, potentially indicating compromised renal balance.

This study revealed that levonorgestrel administration significantly increased malondialdehyde levels in the kidney. Alcohol abuse has also been associated with an increase in malondialdehyde concentration (Moraes et al., 2023), which may be indicative of renal oxidative damage and implicated in renal disease (Sreenivasulu et al., 2020). A significant decrease was observed in the malondialdehyde levels in rats treated with glutathione after levonorgestrel administration compared to rats treated with only levonorgestrel. This is consistent with Tualeka et al. (2019), who stated that glutathione and malondialdehyde levels have a substantial reciprocal correlation.

The decreased superoxide dismutase levels in rats treated with levonorgestrel might indicate lipid peroxidation and oxidative stress (Hamam et al., 2022). 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. This suggests that glutathione has ameliorative effects on levonorgestrel-induced renal damage.

Catalase, an essential enzyme that protects cells from oxidative damage, decreased following levonorgestrel treatment. Similarly, alcohol abuse is associated with a decrease in catalase levels (Moraes et al., 2023). According to Hong and Park (2021), a decrease in catalase levels renders the kidney vulnerable to oxidative tissue damage and renal fibrosis. Our study suggests that glutathione may restore catalase levels depleted by levonorgestrel treatment, protecting renal cells against oxidative damage.

Renal vascular congestion and mild renal tubular necrosis were observed with an increase in the levonorgestrel dosage, which according to Deferrari et al. (2021) may be attributed to drug reactions. Renal congestion reduces blood flow velocity in the peritubular capillaries leading

to acute kidney injury (Kitani et al., 2022). 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 (Tanaka et al., 2020). The reconstitution of normal renal cytoarchitecture and tubules may indicate that glutathione promotes the intrinsic renal repair of levonorgestrel-induced hepatic histological damage.

5. Conclusion

Consistent use of levonorgestrel damages kidney cytology and function, but glutathione treatment may proffer remedy to kidney cytoarchitecture impairments and reduce oxidative stress. Owing to the antioxidant properties of glutathione, the adverse effects of levonorgestrel on the kidney may be alleviated.

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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